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(54) **POLYPEPTIDES AND POLYNUCLEOTIDES, AND USES THEREOF FOR TREATMENT OF IMMUNE RELATED DISORDERS AND CANCER**

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(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

This invention relates to LY6G6F, VSIG10, TMEM25 and LSR proteins, which are suitable targets for immunotherapy, treatment of cancer, infectious disorders, and/or immune related disorders, and drug development. This invention further relates to soluble LY6G6F, VSIG10, TMEM25 and LSR molecules, extracellular domains of LY6G6F, VSIG10, TMEM25 and LSR and conjugates, which are suitable drugs for immunotherapy, treatment of cancer, infectious disorders, and/or immune related disorders. This invention further relates to antibodies and antigen binding fragments and conjugates containing same, and/or alternative scaffolds, specific for LY6G6F, VSIG10, TMEM25 or LSR molecules, which are suitable drugs for immunotherapy, treatment of cancer, infectious disorders, and/or immune related disorders.

12 Claims, 116 Drawing Sheets

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LYG6F- SEQ ID NO:1

MAVLFLLFLCGTPQAADNMQAIYVALGEAVELPCSPPTLHGDEHLSWFCSPAAGSFTTLVAQVQVGRP
APDPGKPGRESRLRLGNYSWLEGSKEEDAGRYWCAVLGQHNYQNWRVYDVLVLKGSQLSARAADGSP
CNVLLCSVVPSSRMDSVTWQEGKGPVRGRVQSEFWGSEAALLLVCPGEGELSEPRSRPRRIIRCLMTHNKG
VSFSLAASIDASPALCAPSTGWDMPWILMLLLTMGQGVVILALSIVLWRQVRGAPGRDASIPQFKPEIQV
YENIHLARLGPPAHKPR

SP - aa 1-16: MAVLFLLFLCGTPQA

TM - aa 235-257: WILMLLLTMGQGVVILALSIVLW

LYG6F ECD (without SP) – aa 17-234 (SEQ ID NO:2):

ADNMQAIYVALGEAVELPCSPPTLHGDEHLSWFCSPAAGSFTTLVAQVQVGRPAPDPGKPGRESRLRL
GNYSWLEGSKEEDAGRYWCAVLGQHNYQNWRVYDVLVLKGSQLSARAADGSPCNVLLCSVVPSSRMD
SVTWQEGKGPVRGRVQSEFWGSEAALLLVCPGEGELSEPRSRPRRIIRCLMTHNKGVSFSLAASIDASP
ALCAPSTGWDMP

NA encoding LYG6F ECD (SEQ ID NO:33):

GCAGACAACATGCAGGCCATCTATGTGGCCTTGGGGGAGGCAGTAGAGCTGCCATGTCCCTCACCACCTA
CTCTACATGGGGACGAACACCTGTCATGGTTCTGCAGCCCTGCAGCAGGCTCCTTCACCACCCTGGTAGC
CCAAGTCCAAGTGGGCAGGCCAGCCCCAGACCCTGGAAAACCAGGAAGGGAATCCAGGCTCAGACTGCTG
GGGAACATATTCTTTGTGGTTGGAGGGATCCAAAGAGGAAGATGCCGGGCGGTACTGGTGCGCTGTGCTAG
GTCAGCACCACAACACTACCAGAACTGGAGGGTGTACGACGTCTTGGTGCTCAAAGGATCCCAGTTATCTGC
AAGGGCTGCAGATGGATCCCCCTGCAATGTCTCTGTGCTCTGTGGTCCCCAGCAGACGCATGGACTCT
GTGACCTGCCAGGAAGGAAGGGTCCCGTGAGGGGCGCTGTTCACTCCTTCTGGGGCAGTGAGGCTGCCC
TGCTCTTGGTGTGTCTGGGGAGGGGCTTTCTGAGCCCAGGAGCCGAAGACCAAGAATCATCCGCTGCCT
CATGACTCACAACAAAGGGTCACTTTAGCCTGGCAGCCTCCATCGATGCTTCTCCTGCCCTCTGTGCC
CCTTCCACGGGCTGGGACATGCCT

FIG. 1A

VSIG10- SEQ ID NO:3

MAAGGSAPEPRVLVCLGALLAGWVAVGLEAVVIGEVHENVTLHCGNISGLRGQVTWYRNNSEPVFLLSSN
SSLRPAEPFSLVDATSLHIESLSLGDEGIYTCQEILNVTQWFOVWLOVASGPYOIEVHIVATGTLPNGT
LYAARGSOVDFSCNSSSRPPPVVEWWFOALNSSSESEFGHNLTVNFFSLLLISPLOGNYTCLALNQLSKR
HRKVTITELLVYYPPPSAPOCWAQMASGSFMLQLTCTRWDDGGYPDPDFLWIEEPGGVIVGKSKLGVEMLS
QLSDGKKFKCVTSHIVGPESGASCMVOIRGPSLLSEPMKTCFTGGNVTLTCOVSGAYPPAKILWLRNLTO
PEVIIQPSSRHLITQDQNSTLTIHNCSDLDDEGYICRADSPVGVREMEIWLSVKEPLNIGG**IVGTIVS**
LLLLGLAIISGLLLHYSPVFCWKVGNTSRGQNMDDVMVLVDSEEEEEEEEEEEEDAAVGEQEGAREREEL
PKEIPKQDHIHRVTALVNGNIEQMGNGFQDLQDSSSEEQSDIVQEEDRPV

SP - aa 1-30: **MAAGGSAPEPRVLVCLGALLAGWVAVGLEA**TM - aa 414-434: **IVGTIVSLLLLGLAIISGLLL**

VSIG10 ECD (without SP) - aa 31-413 (SEQ ID NO:4):

VVIGEVHENVTLHCGNISGLRGQVTWYRNNSEPVFLLSSNSSLRPAEPFSLVDATSLHIESLSLGDEGI
YTCQEILNVTQWFOVWLOVASGPYOIEVHIVATGTLPNGTLYAARGSOVDFSCNSSSRPPPVVEWWFOAL
NSSSESEFGHNLTVNFFSLLLISPLOGNYTCLALNQLSKRHRKVTITELLVYYPPPSAPOCWAQMASGSFM
LQLTCTRWDDGGYPDPDFLWIEEPGGVIVGKSKLGVEMLSSESQSDGKKFKCVTSHIVGPESGASCMVOIRG
PSLLSEPMKTCFTGGNVTLTCOVSGAYPPAKILWLRNLTOPEVIIQPSSRHLITQDQNSTLTIHNCSD
LDEGYICRADSPVGVREMEIWLSVKEPLNIGG

NA encoding VSIG10 ECD (SEQ ID NO:34):

GTTGTCATTGGAGAAGTTCATGAGAATGTTACTCTGCACTGTGGCAACATCTCGGGACTGAGGGGCCAGG
TGACCTGGTACCGGAACAACCTCGAGCCTGTCTTCCTTCTCTCGTCCAACTCTAGCCTCCGCCAGCTGA
GCCTCGCTTCTCTAGTGGATGCCACCTCCCTGCACATTGAATCGCTGAGCCTGGGAGATGAGGGAATC
TACACCTGCCAGGAGATCCTGAATGTGACTCAGTGGTTCCAAGTGTGGCTGCAGGTGGCCAGCGGCCCT
ATCAGATTGAGGTCCACATCGTGGCCACCGGCACACTCCCCAACGGCACCCCTCTATGCAGCCAGGGGCTC
CCAGGTGGACTTCAGCTGCAACAGCAGCTCCAGGCCACCACCCGTGGTTGAATGGTGGTTCCAGGCCCTG
AATTCCAGCAGCGAGTCCCTTTGGCCACAACCTGACAGTCAACTTTTTCTCACTGTTACTGATATCGCCAA
ACCTCCAAGGGAACACACCTGTTTAGCCTTGAATCAGCTCAGCAAGAGACATCGAAAGGTGACCACCGA
GCTCCTGGTCTACTATCCCCCTCCATCAGCTCCCCAGTGTGGGCACAGATGGCATCAGGATCGTTCATG
TTGCAGCTTACCTGTGCTGGGATGGGGGATACCCTGACCCTGACTTCTGTGGATAGAAGAGCCAGGAG
GTGTAATCGTGGGGAAGTCAAAGCTGGGGGTGGAATGCTGAGCGAGTCCCAGCTGTGCGGATGGCAAGAA
GTTCAAGTGTGTTACAAGCCACATAGTTGGGCCAGAGTCGGGCGCCAGCTGCATGGTGCAGATCAGGGGT
CCCTCCCTTCTCTGAGCCCATGAAGACTTGCTTCACTGGGGGCAATGTGACGCTTACATGCCAGGTGT
CTGGGGCCTACCCCCCTGCCAAGATCCTGTGGCTGAGGAACCTTACCCAGCCCAGGTGATCATCCAGCC
TAGCAGCCGCCATCTCATTACCCAGGATGGCCAGAATCCACCCCTCACTATCCACAACCTGCTCCAGGAC
CTGGATGAGGGCTACTACATCTGCCGAGCTGACAGCCCTGTAGGGGTGAGGGAGATGGAAATCTGGCTGA
GTGTGAAAGAACCTTTAAATATCGGGGGG

FIG. 1B

VSIG10 Variant skipping exon 3 (101aa presented in Italic and underlined in the figure above)
(SEQ ID NO:5):

MAAGGSAPEPRVLVCLGALLAGWVAVGLEAVVIGEVHENVTLHCGNISGLRGQVTWYRNNSEPVFLSSN
SSLRPAEPRFSLVDATSLHIESLSLGDEGIYTCQEILNVTQWFQVWLOVANPPPSAPQCWAQMASGSFML
QLTCRWDGGYPDPDFLWIEEPGGVIVGKSKLGVEMLSESQSDGKKFKCVTSHIVGPESGASCMVQIRG
PSLLSEPMKTCFTGGNVTLTQVSGAYPPAKILWLRNLTQPEVIIQPSSRHLITODGONSTLTIHNCSQDL
DEGYIICRADSPVGVREMEIWLSVKEPLNIGG**IVGTIVSLLLLGLAIISGLLL**HYSPTFCWKVGNTSRGQ
NMDDVMVLVDSEEEEEEEEEEEEDAAVGEQEGAREREELPKIIPKQDHIHRVTALVNGNIEQMGNFQDL
QDDSSSEEQSDIVQEEDRPV

SP - aa 1-30: **MAAGGSAPEPRVLVCLGALLAGWVAVGLEA**

TM - aa 313-333: **IVGTIVSLLLLGLAIISGLLL**

VSIG10 Variant skipping exon 3 ECD (without SP) - aa 31-312 (SEQ ID NO:6):

VVIGEVHENVTLHCGNISGLRGQVTWYRNNSEPVFLSSNSSLRPAEPRFSLVDATSLHIESLSLGDEGI
YTCQEILNVTQWFQVWLOVANPPPSAPQCWAQMASGSFMLQLTCRWDGGYPDPDFLWIEEPGGVIVGKSK
LGVEMLSESQSDGKKFKCVTSHIVGPESGASCMVQIRGPSLLSEPMKTCFTGGNVTLTQVSGAYPPAK
ILWLRNLTQPEVIIQPSSRHLITQDQONSTLTIHNCSQDLDEGYIICRADSPVGVREMEIWLSVKEPLNI
GG

FIG. 1C-1

NA encoding VSIG10 Variant skipping exon 3 (SEQ ID NO:35):

ATGGCCGCAGGCGGCAGTGCGCC
GAGCCCCGCGTCTCTGCTCGCCCTCGGGGCGCTCCTGGCCGGCTGGGTGCGCGTAGGATTGGAGGCTGTTG
TCATTGGAGAAGTTCATGAGAATGTTACTCTGCACTGTGGCAACATCTCGGGACTGAGGGGCCAGGTGAC
CTGGTACCGGAACAACCTCGGAGCCTGTCTTCTTCTCTCGTCCAACCTCTAGCCTCCGGCCAGCTGAGCCT
CGCTTCTCTCTAGTGGATGCCACCTCCCTGCACATTGAATCGCTGAGCCTGGGAGATGAGGGAATCTACA
CCTGCCAGGAGATCCTGAATGTGACTCAGTGGTTCCAAGTGTGGCTGCAGGTGGCCAATCCCCCTCCATC
AGCTCCCCAGTGCTGGGCACAGATGGCATCAGGATCGTTCATGTTGCAGCTTACCTGTGCTGGGATGGG
GGATAACCTGACCCTGACTTCTGTGGATAGAAGAGCCAGGAGGTGTAATCGTGGGGAAGTCAAAGCTGG
GGGTGGAAATGCTGAGCGAGTCCAGCTGTCCGATGGCAAGAAGTTCAGTGTGTTACAAGCCACATAGT
TGGGCCAGAGTCGGGCGCCAGCTGCATGGTGCAGATCAGGGGTCCCTCCCTTCTCTGAGCCCATGAAG
ACTTGCTTCACTGGGGGCAATGTGACGCTTACATGCCAGGTGTCTGGGGCCTACCCCCCTGCCAAGATCC
TGTGGCTGAGGAACCTTACCCAGCCCGAGGTGATCATCCAGCCTAGCAGCCGCCATCTCATTACCCAGGA
TGGCCAGAACTCCACCCTCACTATCCACAATGCTCCCAGGACCTGGATGAGGGCTACTACATCTGCCGA
GCTGACAGCCCTGTAGGGGTGAGGGAGATGGAAATCTGGCTGAGTGTGAAAGAACCTTTAAATATCGGGG
GGATTGTGGGAACCATTTGTGAGCCTCCTTCTGCTGGGACTGGCCATTATCTCAGGGCTTCTGTTGCATTA
TAGCCCTGTGTTCTGCTGGAAAGTAGGAAACACTTCCAGGGGACAAAACATGGATGATGTCATGGTTTTG
GTGGATTCAGAAGAGGAAGAGGAGGAGGAGGAGGAGGAGGAAGATGCTGCAGTAGGGGAACAGGAGG
GAGCACGTGAGAGAGAGGAGTTGCCAAAAGAAATACCTAAGCAGGACCACATTACAGAGTGACCGCCTT
GGTGAATGGGAACATAGAACAGATGGGAAATGGATTCCAGGATCTTCAAGATGACAGCAGTGAGGAGCAA
AGTGACATTGTTCAAGAAGAAGACAGGCCAGTCTGA

FIG. 1C-2

NA encoding VSIG10 Variant skipping exon 3 ECD (SEQ ID NO:36):

GTTGTCATTGGAGAAGTTCATGAGAATGTTACTCTGCACTGTGGCAACATCTCGGGACTGAGGGGCCAGG
TGACCTGGTACCGGAACAACCTCGGAGCCTGTCTTCCTTCTCTCGTCCAACTCTAGCCTCCGGCCAGCTGA
GCCTCGCTTCTCTCTAGTGGATGCCACCTCCCTGCACATTGAATCGCTGAGCCTGGGAGATGAGGGAATC
TACACCTGCCAGGAGATCCTGAATGTGACTCAGTGGTTCCAAGTGTGGCTGCAGGTGGCCAATCCCCCTC
CATCAGCTCCCCAGTGCTGGGCACAGATGGCATCAGGATCGTTCATGTTGCAGCTTACCTGTGCTGGGA
TGGGGGATACCCTGACCCTGACTTCCTGTGGATAGAAGAGCCAGGAGGTGTAATCGTGGGGAAGTCAAAG
CTGGGGGTGGAAATGCTGAGCGAGTCCCAGCTGTCCGATGGCAAGAAGTTCAAGTGTGTTACAAGCCACA
TAGTTGGGCCAGAGTCGGGCGCCAGCTGCATGGTGCAGATCAGGGGTCCCTCCCTTCTCTCTGAGCCCAT
GAAGACTTGCTTCACTGGGGGCAATGTGACGCTTACATGCCAGGTGTCTGGGGCTACCCCCCTGCCAAG
ATCCTGTGGCTGAGGAACCTTACCCAGCCCGAGGTGATCATCCAGCCTAGCAGCCGCCATCTCATTACCC
AGGATGGCCAGAACTCCACCCTCACTATCCACAACCTGCTCCAGGACCTGGATGAGGGCTACTACATCTG
CCGAGCTGACAGCCCTGTAGGGGTGAGGGAGATGGAAATCTGGCTGAGTGTGAAAGAACCTTTAAATATC
GGGGGG

FIG. 1C-3

TMEM25 - SEQ ID NO:7

MALPPGPAALRHTTTTLLPALSSGWGELEEPQIDGQTWAERALRENERHAFTCRVAGGPGT
PRLAWYLDGQLQEASTSRLLSVGGEAFSGGTSTFTVTAHRAQHELNCSLQDPRSGRSANA
SVILNVQFKPEIAQVGAKYQEAQGPGLLVVLFALVRANPPANVTWIDQDGPVTVNTSDFL
VLDAQNYPWLTNHTVQLQLRSLAHNLSVVATNDVGVTASLPAPGLLATRVEVPLLGIVV
AAGLALGTLVGFSTLVACLVCRKEKKTGKPSRHPSLISSDSNNLKLNNVRLPRENMSLPS
NLQLNDLTPDSRAVKPADRQMAQNNSRPELLDPEPGGLTSQGFIRLPVLGYIYRVSSVS
SDEIWL

SP - aa 1-26: MALPPGPAALRHTTTTLLPALSSGWTM - aa 233-261: VPLLGIVVAAGLALGTLVGFSTLVACLVC

TMEM25 ECD (without SP) - aa 27-232 (SEQ ID NO:8):

ELEPQIDGQ TWAERALRENERHAFTCRVAGGP GT PRLAWYLDGQLQEASTSRLLSVGGEA
FSGGTSTFTVTAHRAQHELNCSLQDPRSGRSANASVILNVQFKPEIAQVGAKYQEAQGP
GLLVVLFALVRANPPANVTWIDQDGPVTVNTSDFLVLDAQNYPWLTNHTVQLQLRSLAHNLS
VVATNDVGVTASLPAPGLLATRVE

NA encoding TMEM25 ECD (SEQ ID NO:37):

GAGTTGGAGCCACAAATAGATGGTCAGACCTGGGCTGAGCGGGCACTTCGGGAGAATGAACGCCACGC
CTTCACCTGCCGGGTGGCAGGGGGGCTGGCACCCCGAGATTGGCCTGGTATCTGGATGGACAGCTGCA
GGAGGCCAGCACCTCAAGACTGCTGAGCGTGGGAGGGGAGGCCTTCTCTGGAGGCACCAGCACCTTCA
CTGTCACTGCCCATCGGGCCCAGCATGAGCTCAACTGCTCTCTGCAGGACCCAGAAAGTGGCCGATCAGC
CAACGCCTCTGTATCCTTAATGTGCAATTCAAGCCAGAGATTGCCCAAGTCGGCGCCAAGTACCAGGAA
GCTCAGGGCCCAGGCCTCCTGGTTGTCTGTTTGGCCTGGTGCGTGCCAACCCGCCGCCAATGTCACCT
GGATCGACCAGGATGGGCCAGTGACTGTCAACACCTCTGACTTCTGGTGCTGGATGCGCAGAACTACC
CCTGGCTCACCACCCACGGTGCAGCTGCAGCTCCGCAGCCTGGCACACAACCTCTCGGTGGTGGCCAC
CAATGACGTGGGTGTCACCACTGCGTTCAGCCCCAGGGCTTCTGGCTACCCGG

FIG. 1D

LSR isoform-a (SEQ ID NO:11):

MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARAIQVTVSNPYHVVFLEQPVTLPCTYQMTST
PTQPIVIWKYSFCRDRIADAFSPASVDNQLNAQLAAGNPGYNPYVEQDSVRTVRVATKQGNVTLGD
YYQRRITITGNADLTFDQTAWGDSGVYYCSVVSAQDLQGNNEAYAELIVLGRTSGVAELLPGFQAGPIE
DWLFVVVVCLAAFLIFLLLGICWCQCCPHTCCCYVRCPCCPDKCCPEALYAAGKAATSGVPSIYAPSTY
AHLSPAKTPPPAMIPMGPAYNGYPGGYPGDVDRSSSAGGQGSYVPLLRDTSVASEVRSYRIQASQQ
DDSMRVLYMEKELANFDPSPRGPPSGRVERAMSEVTS LHEDDWRSPSRGPALTPIRDEEWGGHSPRSP
RGWDQEPAREQAGGWRARRPRARSDALDDLTTPSTAESGSRSPSTNGGSRAYMPRSPSRDDLYDQD
DSRDFPRSRDPHYDDFRSREPPADPRSHHRTDPRDNGSRSGDLPYDGRLLLEEAVRKKGSEERRRPHK
EEEEAYPPAPPYSETDSQASRERRLKKNLALSRESLVV

SP - aa 1-41: **MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARA**

TM - aa 212-234: **WLFVVVVCLAAFLIFLLLGICWC**

LSR isoform-a ECD (without SP) - aa 42-211 (SEQ ID NO:12):

IQVTVSNPYHVVFLEQPVTLPCTYQMTSTPTQPIVIWKYSFCRDRIADAFSPASVDNQLNAQLAAGNPG
YNPYVEQDSVRTVRVATKQGNVTLGDYYQRRITITGNADLTFDQTAWGDSGVYYCSVVSAQDLQGN
NEAYAELIVLGRTSGVAELLPGFQAGPIED

NA encoding LSR isoform-a ECD (SEQ ID NO:40):

ATCCAGGTGACCGTGTCCAACCCCTACCACGTGGTGATCCTCTTCCAGCCTGTGACCCCTGCCCTGTACCT
ACCAGATGACCTCGACCCCCACGCAACCCATCGTCATCTGGAAGTACAAGTCTTCTGCCGGGACCCCAT
CGCCGATGCCTTCTCCCCGGCCAGCGTCGACAACCAGTCAATGCCAGCTGGCAGCCGGGAACCCAGGC
TACAACCCCTACGTGAGTGCCAGGACAGCGTGCGCACCGTCAGGGTCGTGGCCACCAAGCAGGGCAACG
CTGTGACCCCTGGGAGATTACTACCAGGGCCGGAGGATTACCATCACCGGAAATGCTGACCTGACCTTTGA
CCAGACGGCGTGGGGGGACAGTGGTGTGTATTACTGCTCCGTGGTCTCAGCCCAGGACCTCCAGGGGAAC
AATGAGGCCTACGCAGAGCTCATCGTCCTTGGGAGGACCTCAGGGGTGGCTGAGCTCTTACCTGGTTTTC
AGGCGGGGCCCATAGAAGAC

FIG. 1E

LSR isoform-b, skipping exon 4 (19aa) (SEQ ID NO:13):

MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARAIQVTVSNPYHVILFQPVTLPCITYQMTST
PTQPIVINKYKSFCRDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD
SVRTVRVVKQGNVTLGDIYYQGRRITITGNADLTFDQTAWGDSGVYYCSV
SAQDLQGNNEAYAELIVLD**WLFVVVVCLAAFLIFLLL**
GICWCQCCPHTCCCYVRCPCCPDKCCPEALYAAGKAATSGVPSIYAPSTY
AHLSPAKTPPPAMIPMGPAYNGYPGGYPGDVDRSSAGGQGSYVPLLRDT
DSSVASEVRSYRIQASQQDDSMRVLYMEKELANFDP
SRGPPSGRVERAMSEVTSLEHDDWRSRPSRGPALTPIRDEEWGGHSPRSPRGWDQEPAREQAGGGWRAR
RPRARSVDALDDLTPSTAESGSRSPTSNGGRSRAYMPPRSRSRDDLYDQDDSRDFPRSRDPHYDDFRSR
ERPPADPRSHHRTDRPDNGSRSGDLPYDGRLLLEEAVRKKGSEERRRPHKEEEEEAYPPAPPPYSETD
SQASRERRLKKNLALSRESLVV

SP - aa 1-41: **MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARA**

TM - aa 193-215: **WLFVVVVCLAAFLIFLLLGICWC**

LSR isoform-b ECD (without SP) - aa 42-192 (SEQ ID NO:14):

IQVTVSNPYHVILFQPVTLPCITYQMTSTPTQPIVINKYKSFCRDRIADAFSPASVDNQLNAQLAAGNPG
YNPYVECD SVRTVRVVKQGNVTLGDIYYQGRRITITGNADLTFDQTAWGDSGVYYCSVSAQDLQGN
NEAYAE LIVLD

NA encoding LSR isoform-b ECD (SEQ ID NO:41):

ATCCAGGTGACCGTGTCACCCCTACCAGGTGGTGATCCTCTTCCAGCCTGTGACCCCTGCCCTGTACCT
ACCAGATGACCTCGACCCCCACGCAACCCATCGTCATCTGGAAGTACAAGTCTTTCTGCCGGGACCGCAT
CGCCGATGCCTTCTCCCGGCCAGCGTCGACAACCAGCTCAATGCCAGCTGGCAGCCGGGAACCCAGGC
TACAACCCCTACGTCGAGTGCCAGGACAGCGTGCGACCGTCAGGGTCGTGGCCACCAAGCAGGGCAACG
CTGTGACCCCTGGGAGATTACTACCAGGGCCGGAGGATTACCATCACCGGAAATGCTGACCTGACCTTTGA
CCAGACGGCGTGGGGGACAGTGGTGTGTATTACTGCTCCGTGGTCTCAGCCCAGGACCTCCAGGGGAAC
AATGAGGCCTACGCAGAGCTCATCGTCCTTGAC

FIG. 1F

LSR isoform-c, skipping exons 4 and 5 (19aa and TM) SEQ ID NO:15:

MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARA **QVTVSNPYHVILFQPVTLPCITYQMTST**
PTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECDSVRTVRVVA TKQGNVATLGD
YYQGRRIITITGNADLTDFDQTAWGDSGVYYCSVSAQDLQGNNEAYA **ELIVLVYAAGKAATSGVPSIYAPS**
TYAHLSPAKTPPPPAMIPMGPAINGYPGGYPGDVDRSSAGGQGSYVPLLRDTSSVASEVRSRGYRIQAS
QQDDSMRVLYYMEKELANFDPSPRGPPSGRVERAMSEVTS LHEDDWRSRPSRGPALTPIRDEEWGGHSPR
SPRGWDQEPAREQAGGGWRARRPRARSVDALDDLTPSTAESGSRSPTSNGGRSRAYMPPRSRSRDDLYD
QQDSRDFPRSRDPHYDDFRSRERPPADPRSHHHRTRDPRDNGSRSGDLPYDGRLLLEEAVRKKGSEERRRP
HKEEEEEAYPPAPPYSETDSQASRERRLKKNLALSRESLVV

SP - aa 1-41: **MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARA**

NA encoding LSR isoform-c (SEQ ID NO:42):

ATGGCGCTGTTGGCCGGCGGGCTCTCCAGAGGGCTGGGCTCCCACCCGGCCGCCGAGGCCGGGACGCGG
TCGTCTTCGTGTGGCTTCTGCTTAGCACCTGGTGCACAGCTCCTGCCAGGGCCATCCAGGTGACCGTGTC
CAACCCCTACCACGTGGTGATCCTCTTCCAGCCTGTGACCCCTGCCCTGTACCTACCAGATGACCTCGACC
CCCACGCAACCCATCGTCATCTGGAAGTACAAGTCTTTCTGCCGGGACCGCATCGCCGATGCCCTCTCCC
CGGCCAGCGTCGACAACCAGCTCAATGCCCAGCTGGCAGCCGGGAACCCAGGCTACAACCCCTACGTCGA
GTGCCAGGACAGCGTGCGCACCGTCAGGGTCGTGGCCACCAAGCAGGGCAACGCTGTGACCCCTGGGAGAT
TACTACCAGGGCCGAGGATTACCATCACCGGAAATGCTGACCTGACCTTTGACCAGACGGCGTGGGGGG
ACAGTGGTGTGTATTACTGCTCCGTGGTCTCAGCCCAGGACCTCCAGGGGAACAATGAGGCCTACGCAGA
GCTCATCGTCCTGTGTATGCCGCCGGCAAAGCAGCCACCTCAGGTGTTCCCAGCATTTATGCCCCCAGC
ACCTATGCCACCTGTCTCCCGCCAAGACCCCAACCCCAACAGCTATGATTCCCATGGGCCCTGCCTACA
ACGGGTACCCCTGGAGGATACCCCTGGAGACGTTGACAGGAGTAGCTCAGCTGGTGGCCAAGGCTCCTATGT
ACCCCTGCTTCGGGACACGGACAGCAGTGTGGCCTCTGAAGTCCGCAGTGGCTACAGGATTACAGGCCAGC
CAGCAGGACGACTCCATGCGGGTCCTGTACTACATGGAGAAGGAGCTGGCCAACTTCGACCCTTCTCGAC
CTGGCCCCCCCCAGTGGCCGTGTGGAGCGGGCCATGAGTGAAGTCACCTCCCTCCACGAGGACGACTGGCG
ATCTCGGCCTTCCCGGGGCCCTGCCCTCACCCCGATCCGGGATGAGGAGTGGGTGGCCACTCCCCCGG
AGTCCCAGGGGATGGGACCAGGAGCCCGCCAGGGAGCAGGCAGGCGGGGGCTGGCGGGCCAGGCGGCCCC
GGGCCCCGCTCCGTGGACGCCCTGGACGACCTCACCCCGCGAGCACCGCCGAGTCAGGGAGCAGGTCTCC
CACGAGTAATGGTGGGAGAAGCCGGGCTACATGCCCCCGGAGCCGCAGCCGGGACGACCTCTATGAC
CAAGACGACTCGAGGGAATTCACGCTCCCGGGACCCCACTACGACGACTTCAGGTCTCGGGAGCGCC
CTCCTGCCGACCCSAGTCCCACCACCACCGTACCCGGGACCCCTCGGGACAACGGCTCCAGGTCCGGGGA
CCTCCCCTATGATGGCGGGCTACTGGAGGAGGCTGTGAGGAAGAAGGGTCCGAGGAGAGGAGAGACCC
CACAAGGAGGAGGAGGAAGAGGCCTACTACCCGCCCGCGCCGCCCGCCGCTACTCGGAGACCGACTCGCAGG
CGTCCCAGAGCGCAGGCTCAAGAAGAACTTGGCCCTGAGTCGGGAAAGTTTAGTCGTC

FIG. 1G

LSR isoform-d, skipping exons 4 and 5 (19aa exon + TM + 1aa skip) SEQ ID NO:16:

MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARA **IQVTVSNPYHVILFQPVTLPCTYQMTST**
PTQPIVIWKYKSEFCRDRIADAFSPASVDNQLNAQLAAGNPGYNPYVEQDSVRTVRVVATKQGNVTLGD
YYQGRRITITGNADLTFTDQTAWGDSGVYCSVVSAQDLQGNNEAYAE **ELIVLVYAAGKAATSGVPSIYAPS**
TYAHLSPAKTPPPFAMIPMGPAYNGYPGGYPGDVDRSSSAGGQGSYVPLLRDTSVSVASVRSGYRIQASQ
QDDSMRVLYYMEKELANFDPSPGPPSGRVERAMSEVTS LHEDDWRSRPSRGPALTPIRDEEWGGHSPRS
PRGWDQEPAREQAGGGWRARRPRARSVDALDDLTTPSTAESGSRSPTSNGGRSRAYMPPRSRSRDDLYDQ
DDSRDFPRSRDPHYDDFRSRERPPADPRSHHHRTRDPRDNGSRSGDLPYDGRLLLEEAVRKKGSEERRRPH
KEEEEEAYPPAPPPYSETDSQASRERRLKKNLALSRESLVV

SP - aa 1-41: **MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARA**

NA encoding LSR isoform-d(SEQ ID NO:43):

ATGGCGCTGTTGGCCGGCGGGCTCTCCAGAGGGCTGGGCTCCCACCCGGCCGCCGAGGCCGGGACGCGG
TCGTCTTCGTGTGGCTTCTGCTTAGCACCTGGTGACAGCTCCTGCCAGGGCCATCCAGGTGACCGTGTC
CAACCCCTACCACGTGGTGATCCTCTCCAGCCTGTGACCCTGCCCTGTACCTACCAGATGACCTCGACCC
CCACGCAACCCATCGTCATCTGGAAGTACAAGTCTTTCTGCCGGGACCGCATCGCCGATGCCTTCTCCCC
GGCCAGCGTCGACAACCAGCTCAATGCCAGCTGGCAGCCGGAACCCAGGCTACAACCCCTACGTGGA
GTGCCAGGACAGCGTGCGCACCGTCAGGGTCGTGCCACCAAGCAGGGCAACGCTGTGACCCTGGGAGAT
TACTACCAGGGCCGGAGGATTACCATCACCGAAATGCTGACCTGACCTTTGACCAGACGGCGTGGGGGG
ACAGTGGTGTGTATTACTGCTCCGTGGTCTCAGCCAGGACCTCCAGGGGAACAATGAGGCCTACGCAGA
GCTCATCGTCCTTGTGTATGCCGCCGGCAAAGCAGCCACCTCAGGTGTCCCAGCATTTATGCCCCCAGC
ACCTATGCCACCTGTCTCCCGCAAGACCCCAACCCACCAGCTATGATTCCCATGGGCCCTGCCTACA
ACGGGTACCTGGAGGATACCTGGAGACGTTGACAGGAGTAGCTCAGCTGGTGCCAAAGGCTCCTATGT
ACCCCTGCTTCGGGACACGGACAGCAGTGTGGCCTCTGTCCGAGTGGCTACAGGATTACAGCCAGCCAG
CAGGACGACTCCATGCGGGTCTGTACTACATGGAGAAGGAGCTGGCCAACTTCGACCCTTCTCGACCTG
GCCCCCCCAGTGGCCGTGTGGAGCGGGCCATGAGTGAAGTACCTCCCTCCACGAGGACGACTGGCGATC
TCGGCCTTCCCGGGGCCCTGCCCTACCCCGATCCGGGATGAGGAGTGGGGTGGCCACTCCCCCGGAGT
CCCAGGGGATGGGACCAGGAGCCCGCCAGGGAGCAGGCAGGCGGGGGCTGGCGGGCCAGGCGGGCCCCGGG
CCCGCTCCGTGGACGCCCTGGACGACCTCACCCCGCCGAGACCGCCGAGTCAGGGAGCAGGTCTCCAC
GAGTAATGGTGGGAGAAGCCGGGCCTACATCCCCCGCGGAGCCGCAGCCGGGACGACCTCTATGACCAA
GACGACTCGAGGGACTTCCACGCTCCCGGACCCCCACTACGACGACTTCAGGTCTCGGGAGCGCCCTC
CTGCCGACCCAGGTCCCACCACCACCGTACCCGGGACCTCGGGACAACGGCTCCAGGTCCGGGGACCT
CCCCTATGATGGGCGGCTACTGGAGGAGGCTGTGAGGAAGAAGGGTCCGAGGAGAGGAGAGACCCAC
AAGGAGGAGGAGGAAGAGGCCTACTACCCGCCCGCGCCGCCCGCTACTCGGAGACCGACTCGCAGGCGT
CCCGAGAGCGCAGGCTCAAGAAGAACTTGGCCCTGAGTCGGGAAAGTTTAGTCGTC

FIG. 1H

LSR isoform-e, skipping exons 3, 4 and 5 (40aa exon + 19aa exon+ TM) SEQ ID NO:17:

MALLAGGLSRGLGSHPAAGRDVVFVWLLSTWCTAPARAIQVTVSNPYHVILFQPVTLPCTYQMTST
PTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVEQCDSVRTVRVVKQGNVTLGD
YYQGRITITGMYAAGKAATSGVPSIYAPSTYAHLSPAKTPPPAMIPMGPAYNGYPGGYPGDVDRSSA
GGQGSYVPLLRDTDSSVASEVRSGYRIQASQQDDSMRVLYYMEKELANFDPSPGPPSGRVERAMSEVTS
LHEDDWRSRSPRGALTPIRDEEWGGHSPRSPRGWDQEPAREQAGGWRARRPRARSVDALDDLTPPSTA
ESGSRSPTSNGGRSRAYMPRSRSDLDYDQDDSRDFPRSRDPHYDDFRSRERPPADPRSHHRTDPRD
NGSRSGDLPYDGRLLLEAVRKKGSEERRRPHKEEEEAYYPPAPPYSETDSQASRERRLKKNLALSRES
LVV

SP - aa 1-41: **MALLAGGLSRGLGSHPAAGRDVVFVWLLSTWCTAPARA**

FIG. 1I-1

NA encoding LSR isoform-e (SEQ ID NO:45):

ATGGCGCTGTTGGCCGGCGGGCTCTCCAGAGGGCTGGGCTCCCACCCGGCCGCCGCAGGCCGGGACGCGG
TCGTCTTCGTGTGGCTTCTGCTTAGCACCTGGTGCACAGCTCCTGCCAGGGCCATCCAGGTGACCGTGTG
CAACCCCTACCACGTGGTGATCCTCTTCCAGCCTGTGACCCCTGCCCTGTACCTACCAGATGACCTCGACC
CCCACGCAACCCATCGTCATCTGGAAGTACAAGTCTTTCTGCCGGGACCGCATCGCCGATGCCTTCTCCC
CGGCCAGCGTCGACAACCAGCTCAATGCCACGTGGCAGCCGGGAACCCAGGCTACAACCCCTACGTGCA
GTGCCAGGACAGCGTGCGCACCGTCAGGGTCGTGGCCACCAAGCAGGGCAACGCTGTGACCCCTGGGAGAT
TACTACCAGGGCCGGAGGATTACCATCACCGGAATGTATGCCGCCGGCAAAGCAGCCACCTCAGGTGTTT
CCAGCATTTATGCCCCCAGCACCTATGCCACCTGTCTCCCGCCAAGACCCACCCCCACCAGCTATGAT
TCCCATGGGCCCTGCCTACAACGGGTACCCTGGAGGATAACCCTGGAGACGTTGACAGGAGTAGCTCAGCT
GGTGGCCAAGGCTCCTATGTACCCCTGCTTCGGGACACGGACAGCAGTGTGGCCTCTGAAGTCCGCAGTG
GCTACAGGATTCAGGCCAGCCAGCAGGACGACTCCATGCGGGTCCTGTACTACATGGAGAAGGAGCTGGC
CAACTTCGACCCCTTCTCGACCTGGCCCCCCCCAGTGGCCGTGTGGAGCGGGCCATGAGTGAAGTCACCTCC
CTCCACGAGGACGACTGGCGATCTCGGCCTTCCCGGGGCCCTGCCCTCACCCCGATCCGGGATGAGGAGT
GGGGTGGCCACTCCCCCGGAGTCCCAGGGGATGGGACCAGGAGCCCGCCAGGGAGCAGGCAGGCGGGGG
CTGGCGGGCCAGGCGGGCCCCGGGCCCGCTCCGTGGACGCCCTGGACGACCTCACCCCGCCGAGCACCGCC
GAGTCAGGGAGCAGGTCTCCACGAGTAATGGTGGGAGAAGCCGGGCCTACATGCCCCCGCGGAGCCGCA
GCCGGGACGACCTCTATGACCAAGACGACTCGAGGGACTTCCACGCTCCCGGGACCCCCACTACGACGA
CTTCAGGTCTCGGGAGCGCCCTCCTGCCGACCCAGGTCCCACCACCACCGTACCCGGGACCCCTCGGGAC
AACGGCTCCAGGTCCGGGGACCTCCCCCTATGATGGCGGGCTACTGGAGGAGGCTGTGAGGAAGAAGGGGT
CGGAGGAGAGGAGGAGACCCACAAGGAGGAGGAGGAAGAGGCCTACTACCCGCCCGCGCCGCCCGGTA
CTCGGAGACCGACTCGCAGGCGTCCCGAGAGCGCAGGCTCAAGAAGAAGTGGCCCTGAGTCGGGAAAGT
TTAGTCGTC

FIG. 1I-2

LSR isoform-f, skipping TM, SEQ ID NO:18:

MALLAGGLSRGLGSHPAAGRD**AVFVWLLSTWCTAPARA****IQVT****VS****NPYHV****VILFQ****PVTL****PCTYQMTST**
PTQPI**VIW****KYK****SFC****RD****RIAD****AFSP****ASVD****NQ****LNA****QLA****AGN****PGYN****PYVE****CQDS****VRT****VRV****VAT****KQGN****AVT****LGD**
YYQGR**RITIT****GNAD****LTFD****QTA****WGD****SGV****YYC****SVV****SAQD****LOGN****NEAY****EL****IVL****GRT****SGV****AELL****PGF****QAG****PIE**
VYAAGKAATSGVPSIYAPSTYAHLSPAKTPPPPAMIPMGPAYNGYPGGYPGDVDRSSSAGGQGSYVPLLR
DTDSSVASEVRSGYRIQASQQDDSMRVLYYMEKELANFDPSPRPGPPSGRVERAMSEVTS LHEDDWR SRPS
RGPALTPIRDEEWGGHSPRS PRGWDQEPAREQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPTSNG
GRSRAYMPPRSRSRDDLYDQDDSRDFPRSRDPHYDDFRSRERPPADPRSHHRTDPRDNGSRSGDLPYD
GRLEEAVRKKGSEERRRPHKEEEEAYPPAPPYSETDSQASRERRLKKNLALSRESLVV

SP- aa 1-41: **MALLAGGLSRGLGSHPAAGRD****AVFVWLLSTWCTAPARA**

NA encoding LSR isoform-f (SEQ ID NO:46):

ATGGCGCTGTTGGCCGGCGGGCTCTCCAGAGGGCTGGGCTCCCACCCGGCCGCCGAGGCCGGGACGCGG
TCGTCTTCGTGTGGCTTCTGCTTAGCACCTGGTGCACAGCTCCTGCCAGGGCCATCCAGGTGACCGTGTC
CAACCCCTACCACGTGGTGATCCTCTTCCAGCCTGTGACCCTGCCCTGTACCTACCAGATGACCTCGACC
CCCACGCAACCCATCGTCATCTGGAAGTACAAGTCTTTCTGCCGGGACCGCATCGCCGATGCCTTCTCCC
CGGCCAGCGTCGACAACCAGCTCAATGCCCAGCTGGCAGCCGGAACCCAGGCTACAACCCCTACGTGGA
GTGCCAGGACAGCGTGCGCACCGTCAGGGTCGTGGCCACCAAGCAGGGCAACGCTGTGACCCTGGGAGAT
TACTACCAGGGCCGGAGGATTACCATCACCGGAAATGCTGACCTGACCTTTGACCAGACGGCGTGGGGGG
ACAGTGGTGTGTATTACTGCTCCGTGGTCTCAGCCCAGGACCTCCAGGGGAACAATGAGGCCTACGCAGA
GCTCATCGTCCTTGGGAGGACCTCAGGGGTGGCTGAGCTCTTACCTGGTTTTTCAGGCGGGGCCCATAGAA

FIG. 1J-1

GTGTATGCCGCCGGCAAAGCAGCCACCTCAGGTGTTCCAGCAATTTATGCCCCAGCACCTATGCCACC
TGTCTCCCGCCAAGACCCACCCACCAGCTATGATTCCCATGGGCCCTGCCTACAACGGGTACCCTGG
AGGATACCCTGGAGACGTTGACAGGAGTAGCTCAGCTGGTGGCCAAGGCTCCTATGTACCCCTGCTTCGG
GACACGGACAGCAGTGTGGCCTCTGAAGTCCGCAGTGGCTACAGGATTCAGGCCAGCCAGCAGGACGACT
CCATGCGGGTCCTGTACTACATGGAGAAGGAGCTGGCCAACCTCGACCCCTTCTCGACCTGGCCCCCAG
TGCCCGTGTGGAGCGGGCCATGAGTGAAGTCACCTCCCTCCACGAGGACGACTGGCGATCTCGGCCTCC
CGGGGCCCTGCCCTCACCCCGATCCGGGATGAGGAGTGGGGTGGCCACTCCCCCGGAGTCCCAGGGGAT
GGGACCAGGAGCCCGCCAGGGAGCAGGCAGGCGGGGGCTGGCGGGCCAGGCGGCCCGGGCCCGCTCCGT
GGACGCCCTGGACGACCTCACCCGCCGAGCACCGCCGAGTCAGGGAGCAGGTCTCCACGAGTAATGGT
GGGAGAAGCCGGGCCCTACATGCCCCCGGAGCCGCAGCCGGGACGACCTCTATGACCAAGACGACTCGA
GGGACTTCCCACGCTCCCGGGACCCCACTACGACGACTTCAGGTCTCGGGAGCGCCCTCCTGCCGACCC
CAGGTCCCACCACCACCGTACCCGGGACCTCGGGACAACGGCTCCAGGTCCGGGGACCTCCCCATGAT
GGGCGGCTACTGGAGGAGGCTGTGAGGAAGAAGGGTTCGGAGGAGAGGAGAGACCCACAAGGAGGAGG
AGGAAGAGGCCTACTACCCGCCCGCGCCGCCCGCTACTCGGAGACCGACTCGCAGGCGTCCCGAGAGCG
CAGGCTCAAGAAGAACTTGGCCCTGAGTCGGGAAAGTTTAGTCGTC

FIG. 1J-2

SEQ ID NO:5 (VSIG10_Variant_skipping_exon_3_T95617_P6) versus SEQ ID
NO: 3 (wild type VSIG10, accession number NP_061959.2)

```
1 MAAGGSAPEPRVLVCLGALLAGWVAVGLEAVVIGEVHENVTLHCGNISGL 50
|
|
1 MAAGGSAPEPRVLVCLGALLAGWVAVGLEAVVIGEVHENVTLHCGNISGL 50
. . . . .
51 RGQVTWYRNNSEPVFLLSSNSSLRPAEPRFSLVDATSLHIESLSLGDEGI 100
|
|
51 RGQVTWYRNNSEPVFLLSSNSSLRPAEPRFSLVDATSLHIESLSLGDEGI 100
. . . . .
101 YTCQEILNVTQWFQVWLQVAN..... 121
|
|
101 YTCQEILNVTQWFQVWLQVASGPYQIEVHIVATGTLPNGTLYAARGSQVD 150
. . . . .
121 ..... 121
. . . . .
151 FSCNSSSRPPPVEWWFQALNSSSESFGHNLTVNFFSLLLISPNLQGNYS 200
. . . . .
122 .....PPPSAPQCWAQMASGSFMLQLTCRWDGG 149
|
|
201 CLALNQLSKRHRKVTTELLVYYPPPSAPQCWAQMASGSFMLQLTCRWDGG 250
. . . . .
150 YPDPDFLWIEEPGGVIVGKSKLGVEMLSQSDGKKFKCVTSHIVGPES 199
|
|
```

FIG. 2A-1

251 YPDPDFLWIEEPGGVIVGKSKLGVEMLSQLSDGKKFKCVTSHIVGPES 300

200 GASCMVQIRGPSLLSEPMKTCFTGGNVT LTCQVSGAYPPAKILWLRNLTQ 249

|||||

301 GASCMVQIRGPSLLSEPMKTCFTGGNVT LTCQVSGAYPPAKILWLRNLTQ 350

250 PEVIIQPSSRHLITQDGQNSTLTIHNCSQDLDEGYIICRADSPVGVREME 299

|||||

351 PEVIIQPSSRHLITQDGQNSTLTIHNCSQDLDEGYIICRADSPVGVREME 400

300 IWLSVKEPLNIGGIVGTIVSLLLLGLAIISGLLLHYSPVFCWKVGNTSRG 349

|||||

401 IWLSVKEPLNIGGIVGTIVSLLLLGLAIISGLLLHYSPVFCWKVGNTSRG 450

350 QNMDDVMVLVDSEEEEEEEEEEEEDA AVGEQEGAREREELPKEIPKQDHI 399

|||||

451 QNMDDVMVLVDSEEEEEEEEEEEEDA AVGEQEGAREREELPKEIPKQDHI 500

400 HRVTALVNGNIEQMGNGFQDLQDD SSEEQSDIVQEEDRPV 439

|||||

501 HRVTALVNGNIEQMGNGFQDLQDD SSEEQSDIVQEEDRPV 540

FIG. 2A-2

SEQ ID NO:11 LSR_isoform a versus SEQ ID NO:62 LSR, accession number
NP_991403

Query: 1 MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARAIQVTVSNPYHVVILFQPVT 60
MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARAIQVTVSNPYHVVILFQPVT
Sbjct: 49 MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARAIQVTVSNPYHVVILFQPVT 108

Query: 61 LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD 120
LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD
Sbjct: 109 LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD 168

Query: 121 SVRTVRVVKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYYCSVVSAQDLQG 180
SVRTVRVVKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYYCSVVSAQDLQG
Sbjct: 169 SVRTVRVVKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYYCSVVSAQDLQG 228

Query: 181 NNEAYAEILVLRGTSVGAELLPGFQAGPIEDWLFVVVCLAAFLIFLLLGICWCQCCPHT 240
NNEAYAEILVLRGTSVGAELLPGFQAGPIEDWLFVVVCLAAFLIFLLLGICWCQCCPHT
Sbjct: 229 NNEAYAEILVLRGTSVGAELLPGFQAGPIEDWLFVVVCLAAFLIFLLLGICWCQCCPHT 288

Query: 241 CCCYVRCPCCPDKCCCPEALYAAGKAATSGVPSIYAPSTYAHLSPAKTPPPPAMIPMGPA 300
CCCYVRCPCCPDKCCCPEALYAAGKAATSGVPSIYAPSTYAHLSPAKTPPPPAMIPMGPA
Sbjct: 289 CCCYVRCPCCPDKCCCPEALYAAGKAATSGVPSIYAPSTYAHLSPAKTPPPPAMIPMGPA 348

FIG. 2B-1(1)

Query: 301 YNGYPGGYPGDVDRSSSAGGQGSYVPLLRDTDSSVASEVRSGYRIQASQQDDSMRVLYYM 360
YNGYPGGYPGDVDRSSSAGGQGSYVPLLRDTDSSVASEVRSGYRIQASQQDDSMRVLYYM
Sbjct: 349 YNGYPGGYPGDVDRSSSAGGQGSYVPLLRDTDSSVASEVRSGYRIQASQQDDSMRVLYYM 408

Query: 361 EKELANFDPSRPGPPSGRVERAMSEVTS LHEDDWRSRPSRGPALTPIRDEEWGGHSPRSP 420
EKELANFDPSRPGPPSGRVERAMSEVTS LHEDDWRSRPSRGPALTPIRDEEWGGHSPRSP
Sbjct: 409 EKELANFDPSRPGPPSGRVERAMSEVTS LHEDDWRSRPSRGPALTPIRDEEWGGHSPRSP 468

Query: 421 RGWDQEPAREQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPSTNGGRSRAYMPPRS 480
RGWDQEPAREQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPSTNGGRSRAYMPPRS
Sbjct: 469 RGWDQEPAREQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPSTNGGRSRAYMPPRS 528

Query: 481 RSRDDLYDQDDSRDFPRSRDPHYDDFRSRERPPADPRSHHHRTRDPRDNGSRSGDLPYDG 540
RSRDDLYDQDDSRDFPRSRDPHYDDFRSRERPPADPRSHHHRTRDPRDNGSRSGDLPYDG
Sbjct: 529 RSRDDLYDQDDSRDFPRSRDPHYDDFRSRERPPADPRSHHHRTRDPRDNGSRSGDLPYDG 588

Query: 541 RLLEEAVRKKGSEERRRPHKEEEEEAYPPAPPPYSETDSQASRERRLKKNLALSRESLV 600
RLLEEAVRKKGSEERRRPHKEEEEEAYPPAPPPYSETDSQASRERRLKKNLALSRESLV
Sbjct: 589 RLLEEAVRKKGSEERRRPHKEEEEEAYPPAPPPYSETDSQASRERRLKKNLALSRESLV 648

Query: 601 V 601
V
Sbjct: 649 V 649

FIG. 2B-1(2)

SEQ ID NO:11 LSR_isoform-a versus SEQ ID NO:68 LSR, accession number
XP_002829104, [Pongo abelii]

Query: 1 MALLAGGLSRGLGSHPAAGRDVVFVWLLSTWCTAPARAIQVTVSNPYHVVILEQPV 60
MALLAGGLSRGLGSHPA GRDAVVFVWLLSTWCTAPARAIQVTVSNPYHVVILEQPV
Sbjct: 1 MALLAGGLSRGLGSHPAAPGRDAVVFVWLLSTWCTAPARAIQVTVSNPYHVVILEQPV 60

Query: 61 LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD 120
LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD
Sbjct: 61 LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD 120

Query: 121 SVRTVRVVKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYCSVVSQDLQG 180
SVRTVRVVKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYCSVVSQDLQG
Sbjct: 121 SVRTVRVVKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYCSVVSQDLQG 180

Query: 181 NNEAYAEIVLGRITSGVAELLPGFQAGPIEDWLFVVVCLAAFLIFLLGICWCQCCPHT 240
NNEAYAEIVLGRITSGVAELLPGFQAGP+EDWLFVVVCLAAFLIFLLGICWCQCCPHT
Sbjct: 181 NNEAYAEIVLGRITSGVAELLPGFQAGPMEDWLFVVVCLAAFLIFLLGICWCQCCPHT 240

Query: 241 CCCYVRCPCCPDKCCPEALYAAGKAATSGVPSIYAPSTYHLSPAKTPPPAMIPMGPA 300
CCCYVRCPCCPDKCCPEALYAAGKAATSGVPSIYAPSTYHLSPAKTPPPAMIPMGPA
Sbjct: 241 CCCYVRCPCCPDKCCPEALYAAGKAATSGVPSIYAPSTYHLSPAKTPPPAMIPMGPA 300

FIG. 2B-2(1)

Query: 301 YNGYPGGYPGDVDRSSSAGGQGSYVPLLRDTSSVASEVRSGYRIQASQQDDSMRVLYYM 360
YNGYPGGYPGDVDRSSSAGGQGSYVPLLRDTSSVASEVRSGYRIQASQQDDSMRVLYYM

Sbjct: 301 YNGYPGGYPGDVDRSSSAGGQGSYVPLLRDTSSVASEVRSGYRIQASQQDDSMRVLYYM 360

Query: 361 EKELANFDPSRPGPPSGRVERAMSEVTSIHEDDWRSRPSRGPALTPIRDEEWGGHSPRSP 420
EKELANFDPSRPGPP+GRVERAMSEVTSIHEDDWRSRPSRGPALTPIRDEEWGGHSPRSP

Sbjct: 361 EKELANFDPSRPGPPNGRVERAMSEVTSIHEDDWRSRPSRGPALTPIRDEEWGGHSPRSP 420

Query: 421 RGWDQEPAREQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPSTNGG-RSRAYMPPR 479
RGWDQEP REQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPST+GG R RAYMPPR

Sbjct: 421 RGWDQEPREQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPSTSSGGRRGRAYMPPR 480

Query: 480 SRSRDDLYDQDDSRDFFRSRDPHYDDFRSRERPPADPRSHHHRTRDPRDNGSRSGDLPYD 539
SRSRDDLYDQDDSRDFFRSRD HYDDFRSRERPPADPRSHHHRTRDPRD+GSRSGDL YD

Sbjct: 481 SRSRDDLYDQDDSRDFFRSRDSHYDDFRSRERPPADPRSHHHRTRDPRDHGSRSGDLLYD 540

Query: 540 GRLLAEAVRKKGSEERRRPHKEEEEAYYPAPPYSETDSQASRERRLKKNLALSRESL 599
GRLLAEAVRKKGSEERRRPHKEEEEAYYPAPPYSETDSQASRERRLKKNLALSRESL

Sbjct: 541 GRLLAEAVRKKGSEERRRPHKEEEEAYYPAPPYSETDSQASRERRLKKNLALSRESL 600

Query: 600 VV 601
VV

Sbjct: 601 VV 602

FIG. 2B-2(2)

SEQ ID NO:13 LSR_Isoform_b versus SEQ ID NO:63, LSR accession number
NP_057009

Query: 1 MALLAGGLSRGLGSHPAAGRDVVFVWLLSTWCTAPARAIQVTVSNPYHVVFILFQPV 60
MALLAGGLSRGLGSHPAAGRDVVFVWLLSTWCTAPARAIQVTVSNPYHVVFILFQPV
Sbjct: 49 MALLAGGLSRGLGSHPAAGRDVVFVWLLSTWCTAPARAIQVTVSNPYHVVFILFQPV 108

Query: 61 LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD 120
LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD
Sbjct: 109 LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD 168

Query: 121 SVRTVRVVATKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYYCSVVSQDLQG 180
SVRTVRVVATKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYYCSVVSQDLQG
Sbjct: 169 SVRTVRVVATKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYYCSVVSQDLQG 228

Query: 181 NNEAYAEILVLDWLFVVVVCLAAFLIFLLLGICWCQCCPHTCCCYVRCPCCPDKCCPEA 240
NNEAYAEILVLDWLFVVVVCLAAFLIFLLLGICWCQCCPHTCCCYVRCPCCPDKCCPEA
Sbjct: 229 NNEAYAEILVLDWLFVVVVCLAAFLIFLLLGICWCQCCPHTCCCYVRCPCCPDKCCPEA 288

Query: 241 LYAAGKAATSGVPSIYAPSTYAHLSAKTTPPPAMIPMPAYNGYPGGYPGDVDRSSAG 300
LYAAGKAATSGVPSIYAPSTYAHLSAKTTPPPAMIPMPAYNGYPGGYPGDVDRSSAG
Sbjct: 289 LYAAGKAATSGVPSIYAPSTYAHLSAKTTPPPAMIPMPAYNGYPGGYPGDVDRSSAG 348

FIG. 2C-1(1)

Query: 301 GQGSYVLLRDTDSSVASEVRSGYRIQASQQDDSMRVLYMEKELANFDPSRPGPPSGRV 360
GQGSYVLLRDTDSSVASEVRSGYRIQASQQDDSMRVLYMEKELANFDPSRPGPPSGRV
Sbjct: 349 GQGSYVLLRDTDSSVASEVRSGYRIQASQQDDSMRVLYMEKELANFDPSRPGPPSGRV 408

Query: 361 ERAMSEVTS LHEDDWRSPSRGPALTPIRDEEWGGHSPRSPRGWDQEPAREQAGGGWRAR 420
ERAMSEVTS LHEDDWRSPSRGPALTPIRDEEWGGHSPRSPRGWDQEPAREQAGGGWRAR
Sbjct: 409 ERAMSEVTS LHEDDWRSPSRGPALTPIRDEEWGGHSPRSPRGWDQEPAREQAGGGWRAR 468

Query: 421 RPRARSVDALDDLTPPSTAESGSRSPSTNGGRSRAYMPPRSRSRDDLYDQDDSRDFPRSR 480
RPRARSVDALDDLTPPSTAESGSRSPSTNGGRSRAYMPPRSRSRDDLYDQDDSRDFPRSR
Sbjct: 469 RPRARSVDALDDLTPPSTAESGSRSPSTNGGRSRAYMPPRSRSRDDLYDQDDSRDFPRSR 528

Query: 481 DPHYDDFRSRERPPADPRSHHHRTRDPRDNGSRSGDLPYDGRLLLEEAVRKKGSEERRRPH 540
DPHYDDFRSRERPPADPRSHHHRTRDPRDNGSRSGDLPYDGRLLLEEAVRKKGSEERRRPH
Sbjct: 529 DPHYDDFRSRERPPADPRSHHHRTRDPRDNGSRSGDLPYDGRLLLEEAVRKKGSEERRRPH 588

Query: 541 KEEEEAYYPAPPYPSETDSQASRERRLKKNLALSRESLVV 582
KEEEEEAYYPAPPYPSETDSQASRERRLKKNLALSRESLVV
Sbjct: 589 KEEEEAYYPAPPYPSETDSQASRERRLKKNLALSRESLVV 630

FIG. 2C-1(2)

SEQ ID NO:13 LSR_Isoform_b versus SEQ ID NO:65, LSR, accession number
BAC11614

Query: 1 MALLAGGLSRGLGSHPAAGRDAVFVWLLSTWCTAPARAIQVTVSNPYHVILFQPV 60
MALLAGGLSRGLGSHPAAGRDAVFVWLLSTWCTAPARAIQVTVSNPYHVILFQPV
Sbjct: 1 MALLAGGLSRGLGSHPAAGRDAVFVWLLSTWCTAPARAIQVTVSNPYHVILFQPV 60

Query: 61 LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD 120
LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD
Sbjct: 61 LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD 120

Query: 121 SVRTVRVVKQGNVTLGDYYQGRITITGNADLTDFDQTAWGDSGVYCSVSAQDLQ 180
SVRTVRVVKQGNVTLGDYYQGRITITGNADLTDFDQTAWGDSGVYCSVSAQDLQ
Sbjct: 121 SVRTVRVVKQGNVTLGDYYQGRITITGNADLTDFDQTAWGDSGVYCSVSAQDLQ 180

Query: 181 NNEAYAEILVLDWLFVVVCLAAFLIFLLLGICWCQCCPHTCCCVRCPCCPDKCCPEA 240
NNEAYAEILVLDWLFVVVCLAAFLIFLLLGICWCQCCPHTCCCVRCPCCPDKCCPEA
Sbjct: 181 NNEAYAEILVLDWLFVVVCLAAFLIFLLLGICWCQCCPHTCCCVRCPCCPDKCCPEA 240

Query: 241 LYAAGKAATSGVPSIYAPSTYAHLSPAKTPPPPAMIPMPAYNGYPGGYPGDVDRSSAG 300
LYAAGKAATSGVPSIYAPSTYAHLSPAKTPPPPAMIPMPAYNGYPGGYPGDVDR+SSAG
Sbjct: 241 LYAAGKAATSGVPSIYAPSTYAHLSPAKTPPPPAMIPMPAYNGYPGGYPGDVDRNSSAG 300

FIG. 2C-2(1)

Query: 301 GQGSYVLLRDTSSVASEVRSGYRIQASQQDDSMRVLYMEKELANFDPSRPGPPSGRV 360
GQGSYVLLRDTSSVASEVRSGYRIQASQQDDSMRVLYMEKELANFDPSRPGPPSGRV
Sbjct: 301 GQGSYVLLRDTSSVASEVRSGYRIQASQQDDSMRVLYMEKELANFDPSRPGPPSGRV 360

Query: 361 ERAMSEVTS LHEDDWRSRPSRGPALTPIRDEEWGGHSPRSRPGWDQEPAREQAGGGWRAR 420
ERAMSEVTS LHEDDWRSRPSRGPALTPIRDEEWGGHSPRSRPGWDQEPAREQAGGGWRAR
Sbjct: 361 ERAMSEVTS LHEDDWRSRPSRGPALTPIRDEEWGGHSPRSRPGWDQEPAREQAGGGWRAR 420

Query: 421 RPRARSVDALDDLTPPSTAESGSRSPSTNGG-RSRAYMPPRSRSRDDLYDQDDSRDFPRS 479
RPRARSVDALDDLTPPSTAESGSRSPSTNGG RSRAYMPPRSRSRDDLYDQDDSRDFPRS
Sbjct: 421 RPRARSVDALDDLTPPSTAESGSRSPSTNGGRSRAYMPPRSRSRDDLYDQDDSRDFPRS 480

Query: 480 RDPHYDDFRSRERPPADPRSHHHRTDPRDNGSRSGDLPYDGRLLLEEAVRKKGSEERRRP 539
RDPHYDDFRSRERPPADPRSHHHRTDPRDNGSRSGDLPYDGRLLLEEAVRKKGSEERRRP
Sbjct: 481 RDPHYDDFRSRERPPADPRSHHHRTDPRDNGSRSGDLPYDGRLLLEEAVRKKGSEERRRP 540

Query: 540 HKEEEEEAYYPAPPPYSETDSQASRERRLKKNLALSRESLVV 582
HKEEEEEAYYPAPPPYSETDSQASRERRLKKNLALSRESLVV
Sbjct: 541 HKEEEEEAYYPAPPPYSETDSQASRERRLKKNLALSRESLVV 583

FIG. 2C-2(2)

SEQ ID NO:15 LSR_Isoform_c versus SEQ ID NO:66 LSR, accession number:
NP_991404

Query: 1 MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARAIQVTVSNPYHVVILFQPVT 60
MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARAIQVTVSNPYHVVILFQPVT
Sbjct: 49 MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARAIQVTVSNPYHVVILFQPVT 108

Query: 61 LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD 120
LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD
Sbjct: 109 LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD 168

Query: 121 SVRTVRVVKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYCSVVSQDLQG 180
SVRTVRVVKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYCSVVSQDLQG
Sbjct: 169 SVRTVRVVKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYCSVVSQDLQG 228

Query: 181 NNEAYAELIVLVYAAGKAATSGVPSIYAPSTYAHLSPAKTPPPPAMIPMPAYNGYPGGY 240
NNEAYAELIVLVYAAGKAATSGVPSIYAPSTYAHLSPAKTPPPPAMIPMPAYNGYPGGY
Sbjct: 229 NNEAYAELIVLVYAAGKAATSGVPSIYAPSTYAHLSPAKTPPPPAMIPMPAYNGYPGGY 288

FIG. 2D-1(1)

Query: 241 PGDVDRSSSAGGQGSYVPLLRDTDSSVASEVRSGYRIQASQQDDSMRVLYYMEKELANFD 300
PGDVDRSSSAGGQGSYVPLLRDTDSSVASEVRSGYRIQASQQDDSMRVLYYMEKELANFD
Sbjct: 289 PGDVDRSSSAGGQGSYVPLLRDTDSSVASEVRSGYRIQASQQDDSMRVLYYMEKELANFD 348

Query: 301 PSRPGPPSGRVERAMSEVTS LHEDDWRSRPSRGPALTPIRDEEWGGHSPRSPRGWDQEPA 360
PSRPGPPSGRVERAMSEVTS LHEDDWRSRPSRGPALTPIRDEEWGGHSPRSPRGWDQEPA
Sbjct: 349 PSRPGPPSGRVERAMSEVTS LHEDDWRSRPSRGPALTPIRDEEWGGHSPRSPRGWDQEPA 408

Query: 361 REQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPTSNGGRSRAYMPPRSRSRDDLYD 420
REQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPTSNGGRSRAYMPPRSRSRDDLYD
Sbjct: 409 REQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPTSNGGRSRAYMPPRSRSRDDLYD 468

Query: 421 QDDSRDFPRSRDPHYDDFRSRERPPADPRSHHHRTRDPRDNGSRSGDLPYDCRLLEEAVR 480
QDDSRDFPRSRDPHYDDFRSRERPPADPRSHHHRTRDPRDNGSRSGDLPYDCRLLEEAVR
Sbjct: 469 QDDSRDFPRSRDPHYDDFRSRERPPADPRSHHHRTRDPRDNGSRSGDLPYDCRLLEEAVR 528

Query: 481 KKGSEERRRPHKEEEEAYYPAPPPYSETDSQASRERRLKKNLALSRESLVV 533
KKGSEERRRPHKEEEEAYYPAPPPYSETDSQASRERRLKKNLALSRESLVV
Sbjct: 529 KKGSEERRRPHKEEEEAYYPAPPPYSETDSQASRERRLKKNLALSRESLVV 581

FIG. 2D-1(2)

SEQ ID NO:15 LSR_Isoform_c versus SEQ ID NO:69 LSR, accession number:
XP_002829105.1, [Pongo abelii]

Query: 1 MALLAGGLSRGLGSHPAAGRDAVVFVWLLLSTWCTAPARAIQVTVSNPYHVILFQPV 60
MALLAGGLSRGLGSHPAAGRDAVVFVWLLLSTWCTAPARAIQVTVSNPYHVILFQPV

Sbjct: 1 MALLAGGLSRGLGSHPAAGRDAVVFVWLLLSTWCTAPARAIQVTVSNPYHVILFQPV 60

Query: 61 LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECQD 120
LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECQD

Sbjct: 61 LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECQD 120

Query: 121 SVRTVRVVKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYCSVSAQDLQG 180
SVRTVRVVKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYCSVSAQDLQG

Sbjct: 121 SVRTVRVVKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYCSVSAQDLQG 180

Query: 181 NNEAYAELIVLVYAAGKAATSGVPSIYAPSTYHLSPAKTPPPAMIPMPAYNGYPGGY 240
NNEAYAELIVLVYAAGKAATSGVPSIYAPSTYHLSPAKTPPPAMIPMPAYNGYPGGY

Sbjct: 181 NNEAYAELIVLVYAAGKAATSGVPSIYAPSTYHLSPAKTPPPAMIPMPAYNGYPGGY 240

FIG. 2D-2(1)

Query: 241 PGDVRSSSAGGQGSYVLLRDTDSSVASEVRSGYRIQASQDDSMRVLYYMEKELANFD 300
PGDVRSSSAGGQGSYVLLRDTDSSVASEVRSGYRIQASQDDSMRVLYYMEKELANFD
Sbjct: 241 PGDVRSSSAGGQGSYVLLRDTDSSVASEVRSGYRIQASQDDSMRVLYYMEKELANFD 300

Query: 301 PSRPGPPSGRVERAMSEVTS LHEDDWSRPSRGPALTPIRDEEWGCHSPRSPRGWDQEPA 360
PSRPGPP+GRVERAMSEVTS LHEDDWSRPSRGPALTPIRDEEWGCHSPRSPRGWDQEP
Sbjct: 301 PSRPGPPNGRVERAMSEVTS LHEDDWSRPSRGPALTPIRDEEWGCHSPRSPRGWDQEPP 360

Query: 361 REQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPTSNGG-RSRAYMPPRSRSRDDLY 419
REQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPTS+GG R RAYMPPRSRSRDDLY
Sbjct: 361 REQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPTS+GGRRGRAYMPPRSRSRDDLY 420

Query: 420 DQDDSRDFPRS RDPHYDDFRSRERPPADPRSHHHRTRDPRDNGSRSGDLPYDGRLLLEEAV 479
DQDDSRDFPRS RDPHYDDFRSRERPPADPRSHHHRTRDPRD+GSRSGDLPYDGRLLLEEAV
Sbjct: 421 DQDDSRDFPRS RDSHYDDFRSRERPPADPRSHHHRTRDPRDHGSRSGDLPYDGRLLLEEAV 480

Query: 480 RKKGSEERRRPHKEEEEEAYYPAPPYSETDSQASRERRLKKNLALSRESLVV 533
RKKGSEERRRPHKEEEEEAYYPAPPYSETDSQASRERRLKKNLALSRESLVV
Sbjct: 481 RKKGSEERRRPHKEEEEEAYYPAPPYSETDSQASRERRLKKNLALSRESLVV 534

FIG. 2D-2(2)

SEQ ID NO: 16 LSR_Isoform_d_secreted_R36881_P20 versus SEQ ID NO: 66 LSR
accession number: NP_991404

Query: 1 MALLAGGLSRGLGSHPAAGRDVVFVWLLSTWCTAPARAIQVTVSNPYHVVFILFQPV 60

MALLAGGLSRGLGSHPAAGRDVVFVWLLSTWCTAPARAIQVTVSNPYHVVFILFQPV

Sbjct: 49 MALLAGGLSRGLGSHPAAGRDVVFVWLLSTWCTAPARAIQVTVSNPYHVVFILFQPV 108

Query: 61 LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD 120

LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD

Sbjct: 109 LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD 168

Query: 121 SVRTVRVVATKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYYCSVSAQDLQ 180

SVRTVRVVATKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYYCSVSAQDLQ

Sbjct: 169 SVRTVRVVATKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYYCSVSAQDLQ 228

Query: 181 NNEAYAELIVLVYAAGKAATSGVPSIYAPSTYHLSPAKTPPPPAMIPMPAYNGYPGGY 240

NNEAYAELIVLVYAAGKAATSGVPSIYAPSTYHLSPAKTPPPPAMIPMPAYNGYPGGY

Sbjct: 229 NNEAYAELIVLVYAAGKAATSGVPSIYAPSTYHLSPAKTPPPPAMIPMPAYNGYPGGY 288

FIG. 2E-1(1)

Query: 241 PGDVDRSSSAGGQGSYVPLLRDTSSVAS-VRSGYRIQASQQDDSMRVLYYMEKELANFD 299
PGDVDRSSSAGGQGSYVPLLRDTSSVAS VRSGYRIQASQQDDSMRVLYYMEKELANFD
Sbjct: 289 PGDVDRSSSAGGQGSYVPLLRDTSSVASEVRSGYRIQASQQDDSMRVLYYMEKELANFD 348

Query: 300 PSRPGPPSGRVERAMSEVTS LHEDDWRSRPSRGPALTPIRDEEWGGHSPRSPRGWDQEPA 359
PSRPGPPSGRVERAMSEVTS LHEDDWRSRPSRGPALTPIRDEEWGGHSPRSPRGWDQEPA
Sbjct: 349 PSRPGPPSGRVERAMSEVTS LHEDDWRSRPSRGPALTPIRDEEWGGHSPRSPRGWDQEPA 408

Query: 360 REQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPTSNGGRSRAYMPPRSRSDDLVD 419
REQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPTSNGGRSRAYMPPRSRSDDLVD
Sbjct: 409 REQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPTSNGGRSRAYMPPRSRSDDLVD 468

Query: 420 QDDSRDFPRSRDPHYDDFRSRERPPADPRSHHHRTDPRDNGSRSGDLPYDGRLLLEEAVR 479
QDDSRDFPRSRDPHYDDFRSRERPPADPRSHHHRTDPRDNGSRSGDLPYDGRLLLEEAVR
Sbjct: 469 QDDSRDFPRSRDPHYDDFRSRERPPADPRSHHHRTDPRDNGSRSGDLPYDGRLLLEEAVR 528

Query: 480 KKGSEERRRPHKEEEEEAYYPPAPPPYSETDSQASRERRLKKNLALSRESLVV 532
KKGSEERRRPHKEEEEEAYYPPAPPPYSETDSQASRERRLKKNLALSRESLVV
Sbjct: 529 KKGSEERRRPHKEEEEEAYYPPAPPPYSETDSQASRERRLKKNLALSRESLVV 581

FIG. 2E-1(2)

SEQ ID NO: 16 LSR_Isoform_d_secreted_R36881_P20 versus SEQ ID NO:69
LSR, accession number: XP_002829105.1, [Pongo abelii]

Query: 1 MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARAIQVTVSNPYHVVFILFQPVT 60
MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARAIQVTVSNPYHVVFILFQPVT
Sbjct: 1 MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARAIQVTVSNPYHVVFILFQPVT 60

Query: 61 LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD 120
LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD
Sbjct: 61 LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD 120

Query: 121 SVRTVRVATKQGNVTLGDYYQRRITITGNADLTFDQTAWGDSGVYCSVVSAQDLQG 180
SVRTVRVATKQGNVTLGDYYQRRITITGNADLTFDQTAWGDSGVYCSVVSAQDLQG
Sbjct: 121 SVRTVRVATKQGNVTLGDYYQRRITITGNADLTFDQTAWGDSGVYCSVVSAQDLQG 180

Query: 181 NNEAYAELIVLVYAAGKAATSGVPSIYAPSTYHLSPAKTPPPAMIPMPAYNGYPGGY 240
NNEAYAELIVLVYAAGKAATSGVPSIYAPSTYHLSPAKTPPPAMIPMPAYNGYPGGY
Sbjct: 181 NNEAYAELIVLVYAAGKAATSGVPSIYAPSTYHLSPAKTPPPAMIPMPAYNGYPGGY 240

Query: 241 PGDVRSSSAGGQGSYVPLLRDTDSVAS-VRSGYRIQASQDDSMRVLYMEKELANFD 299
PGDVRSSSAGGQGSYVPLLRDTDSVAS VRSGYRIQASQDDSMRVLYMEKELANFD
Sbjct: 241 PGDVRSSSAGGQGSYVPLLRDTDSVASVRSGYRIQASQDDSMRVLYMEKELANFD 300

FIG. 2E-2(1)

Query: 300 PSRPGPPSGRVERAMSEVTSIHEDDWSRPSRGPALTPIRDEEWGGHSPRSPRGWDQEPA 359
PSRPGPP+GRVERAMSEVTSIHEDDWSRPSRGPALTPIRDEEWGGHSPRSPRGWDQEP

Sbjct: 301 PSRPGPPNGRVERAMSEVTSIHEDDWSRPSRGPALTPIRDEEWGGHSPRSPRGWDQEPP 360

Query: 360 REQAGGGWRARRPRARSVDALDDLTTPSTAESGSRSPSTNGG-RSRAYMPPRSRSRDDLY 418
REQAGGGWRARRPRARSVDALDDLTTPSTAESGSRSPST+GG R RAYMPPRSRSRDDLY

Sbjct: 361 REQAGGGWRARRPRARSVDALDDLTTPSTAESGSRSPSTSSGRRGRAYMPPRSRSRDDLY 420

Query: 419 DQDDSRDFPRSRDPHYDDFRSRERPPADPRSHHHRTRDPRDNGSRSGDLPYDGRLLLEEAV 478
DQDDSRDFPRSRD HYDDFRSRERPPADPRSHHHRTRDPRD+GSRSGDL YDGRLLLEEAV

Sbjct: 421 DQDDSRDFPRSRDSHYDDFRSRERPPADPRSHHHRTRDPRDHGSRSGDLLYDGRLLLEEAV 480

Query: 479 RKKGSEERRRPHKEEEEEAYYPAPPPYSETDSQASRERRLKKNLALSRESLVV 532
RKKGSEERRRPHKEEEEEAYYPAPPPYSETDSQASRERRLKKNLALSRESLVV

Sbjct: 481 RKKGSEERRRPHKEEEEEAYYPAPPPYSETDSQASRERRLKKNLALSRESLVV 534

FIG. 2E-2(2)

SEQ ID NO:17 LSR_Isoform_e_secreted_R36881_P27 versus SEQ ID NO:67,
accession number BAG59226.1

Query: 1 MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARAIQVTVSNPYHVVILFQPVT 60
MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARAIQVTVSNPYHVVILFQPVT
Sbjct: 1 MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARAIQVTVSNPYHVVILFQPVT 60

Query: 61 LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQINAQLAAGNPGYNPYVECD 120
LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQINAQLAAGNPGYNPYVECD
Sbjct: 61 LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQINAQLAAGNPGYNPYVECD 120

Query: 121 SVRTVRVVATKQGNVTLGDYYQGRITITGMYAAGKAATSGVPSIYAPSTYHLSPAKT 180
SVRTVRVVATKQGNVTLGDYYQGRITITGMYAAGKAATSGVPSIYAPSTYHLSPAKT
Sbjct: 121 SVRTVRVVATKQGNVTLGDYYQGRITITGMYAAGKAATSGVPSIYAPSTYHLSPAKT 180

Query: 181 PPPPAMIPMPAYNGYPGGYPGDVDRSSAGGQGSYVPLLRTDSSVASEVRSGYRIQAS 240
PPPPAMIPMPAYNGYPGGYPGDVDRSSAGGQGSYVPLLRTDSSVASEVRSGYRIQAS
Sbjct: 181 PPPPAMIPMPAYNGYPGGYPGDVDRSSAGGQGSYVPLLRTDSSVASEVRSGYRIQAS 240

FIG. 2F-1

Query: 241 QQDDSMRVLYYMEKELANFDPSRPGPPSGRVERAMSEVTS LHEDDWR SRPSRGPALTPIR 300
QQDDSMRVLYYMEKELANFDPSRPGPPSGRVERAMSEVTS LHEDDWR SRPSRGPALTPIR
Sbjct: 241 QQDDSMRVLYYMEKELANFDPSRPGPPSGRVERAMSEVTS LHEDDWR SRPSRGPALTPIR 300

Query: 301 DEEWGGHSPRSPRGWDQEPAREQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPSTN 360
DEEWGGHSPRSPRGWDQEPAREQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPSTN
Sbjct: 301 DEEWGGHSPRSPRGWDQEPAREQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPSTN 360

Query: 361 GGRSRAYMPPRSRSRDDLYDQDDSRDFPRS RDPHYDDFRSRERPPADPRSHHHRTDPRD 420
GGRSRAYMPPRSRSRDDLYDQDDSRDFPRS RDPHYDDFRSRERPPADPRSHHHRTDPRD
Sbjct: 361 GGRSRAYMPPRSRSRDDLYDQDDSRDFPRS RDPHYDDFRSRERPPADPRSHHHRTDPRD 420

Query: 421 NGSRS GDLPYDGRLL EEA VRKKGSEERRRPHKEEEEEAYYP PAPPYPYSETDSQASRERRL 480
NGSRS GDLPYDGRLL EEA VRKKGSEERRRPHKEEEEEAYYP PAPPYPYSETDSQASRERRL
Sbjct: 421 NGSRS GDLPYDGRLL EEA VRKKGSEERRRPHKEEEEEAYYP PAPPYPYSETDSQASRERRL 480

Query: 481 KKNLALSRESLVV 493
KKNLALSRESLVV
Sbjct: 481 KKNLALSRESLVV 493

FIG. 2F-2

SEQ ID NO: 18 LSR_Isoform_f_secreted_R36881_P14 versus SEQ ID NO:62,
LSR, accession number: NP_991403

Query: 1 MALLAGGLSRGLGSHPAAGRDVVFVWLLSTWCTAPARAIQVTVSNPYHVVFVILEQFVT 60
MALLAGGLSRGLGSHPAAGRDVVFVWLLSTWCTAPARAIQVTVSNPYHVVFVILEQFVT
Sbjct: 49 MALLAGGLSRGLGSHPAAGRDVVFVWLLSTWCTAPARAIQVTVSNPYHVVFVILEQFVT 108

Query: 61 LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD 120
LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD
Sbjct: 109 LPCTYQMTSTPTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD 168

Query: 121 SVRTVRVVATKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYCSVSAQDLQG 180
SVRTVRVVATKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYCSVSAQDLQG
Sbjct: 169 SVRTVRVVATKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYCSVSAQDLQG 228

Query: 181 NNEAYAEILVLGRTSGVAELLPGFQAGPIE----- 210
NNEAYAEILVLGRTSGVAELLPGFQAGPIE
Sbjct: 229 NNEAYAEILVLGRTSGVAELLPGFQAGPIEDWLFVVVCLAAFLIFLLLGICWCQCCPHT 288

Query: 211 -----VYAAGKAATSGVPSIYAPSTYAHLSPAKTPPPPAMIPMGPA 251
+YAAGKAATSGVPSIYAPSTYAHLSPAKTPPPPAMIPMGPA
Sbjct: 289 CCCYVRCPCCPDKCCPEALYAAGKAATSGVPSIYAPSTYAHLSPAKTPPPPAMIPMGPA 348

FIG. 2G-1(1)

Query: 252 YNGYPGGYPGDVDRSSSAGGQGSYVPLLRTDSSVASEVRSGYRIQASQQDDSMRVLYYM 311
YNGYPGGYPGDVDRSSSAGGQGSYVPLLRTDSSVASEVRSGYRIQASQQDDSMRVLYYM

Sbjct: 349 YNGYPGGYPGDVDRSSSAGGQGSYVPLLRTDSSVASEVRSGYRIQASQQDDSMRVLYYM 408

Query: 312 EKELANFDPSRPGPPSGRVERAMSEVTS LHEDDWRSRPSRGPALTPIRDEEWGGHSPRSP 371
EKELANFDPSRPGPPSGRVERAMSEVTS LHEDDWRSRPSRGPALTPIRDEEWGGHSPRSP

Sbjct: 409 EKELANFDPSRPGPPSGRVERAMSEVTS LHEDDWRSRPSRGPALTPIRDEEWGGHSPRSP 468

Query: 372 RGWDQEPAREQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPSTNGGRSRAYMPPRS 431
RGWDQEPAREQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPSTNGGRSRAYMPPRS

Sbjct: 469 RGWDQEPAREQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPSTNGGRSRAYMPPRS 528

Query: 432 RSRDDLQDDSRDFPRSRDPHYDDFRSRRERPPADPRSHHHRTRDPRDNGSRSGDLPYDG 491
RSRDDLQDDSRDFPRSRDPHYDDFRSRRERPPADPRSHHHRTRDPRDNGSRSGDLPYDG

Sbjct: 529 RSRDDLQDDSRDFPRSRDPHYDDFRSRRERPPADPRSHHHRTRDPRDNGSRSGDLPYDG 588

Query: 492 RLLEEAVRKKGSEERRRPHKEEEEAYYPPAPPYSETDSQASRERRLKKNLALSRESLV 551
RLLEEAVRKKGSEERRRPHKEEEEAYYPPAPPYSETDSQASRERRLKKNLALSRESLV

Sbjct: 589 RLLEEAVRKKGSEERRRPHKEEEEAYYPPAPPYSETDSQASRERRLKKNLALSRESLV 648

Query: 552 V 552

V

Sbjct: 649 V 649

FIG. 2G-1(2)

SEQ ID NO: 18 LSR_Isoform_f_secreted_R36881_P14 versus SEQ ID NO:66,
LSR, accession number: NP_991404

Query: 1 MALLAGGLSRGLGSHPAAGRDVVFVWLLSTWCTAPARAIQVTVSNPYHVVFILFQPV 60
MALLAGGLSRGLGSHPAAGRDVVFVWLLSTWCTAPARAIQVTVSNPYHVVFILFQPV
Sbjct: 49 MALLAGGLSRGLGSHPAAGRDVVFVWLLSTWCTAPARAIQVTVSNPYHVVFILFQPV 108

Query: 61 LPCTYQMTSTPTQPIVIWKYKSFCRDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD 120
LPCTYQMTSTPTQPIVIWKYKSFCRDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD
Sbjct: 109 LPCTYQMTSTPTQPIVIWKYKSFCRDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECD 168

Query: 121 SVRTVRVVATKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYCSVVSAQDLQG 180
SVRTVRVVATKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYCSVVSAQDLQG
Sbjct: 169 SVRTVRVVATKQGNVTLGDYYQGRITITGNADLTFDQTAWGDSGVYCSVVSAQDLQG 228

Query: 181 NNEAYAEIVL **GRTSGVAELLPGFQAGPIE** VYAAGKAATSGVPSIYAPSTYAHLSPAKTP 240
NNEAYAEIVL VYAAGKAATSGVPSIYAPSTYAHLSPAKTP
Sbjct: 229 NNEAYAEIVL-----VYAAGKAATSGVPSIYAPSTYAHLSPAKTP 269

Query: 241 PPPAMIPMGPAYNGYPGGYPGDVDRSSSAGGQGSYVPLLRDTDSSVASEVRSGYRIQASQ 300
PPPAMIPMGPAYNGYPGGYPGDVDRSSSAGGQGSYVPLLRDTDSSVASEVRSGYRIQASQ
Sbjct: 270 PPPAMIPMGPAYNGYPGGYPGDVDRSSSAGGQGSYVPLLRDTDSSVASEVRSGYRIQASQ 329

FIG. 2G-2(1)

Query: 301 QDDSMRVLYYMEKELANFDPSRPGPPSGRVERAMSEVTS LHEDDWRSRPSRGPALTPIRD 360
QDDSMRVLYYMEKELANFDPSRPGPPSGRVERAMSEVTS LHEDDWRSRPSRGPALTPIRD
Sbjct: 330 QDDSMRVLYYMEKELANFDPSRPGPPSGRVERAMSEVTS LHEDDWRSRPSRGPALTPIRD 389

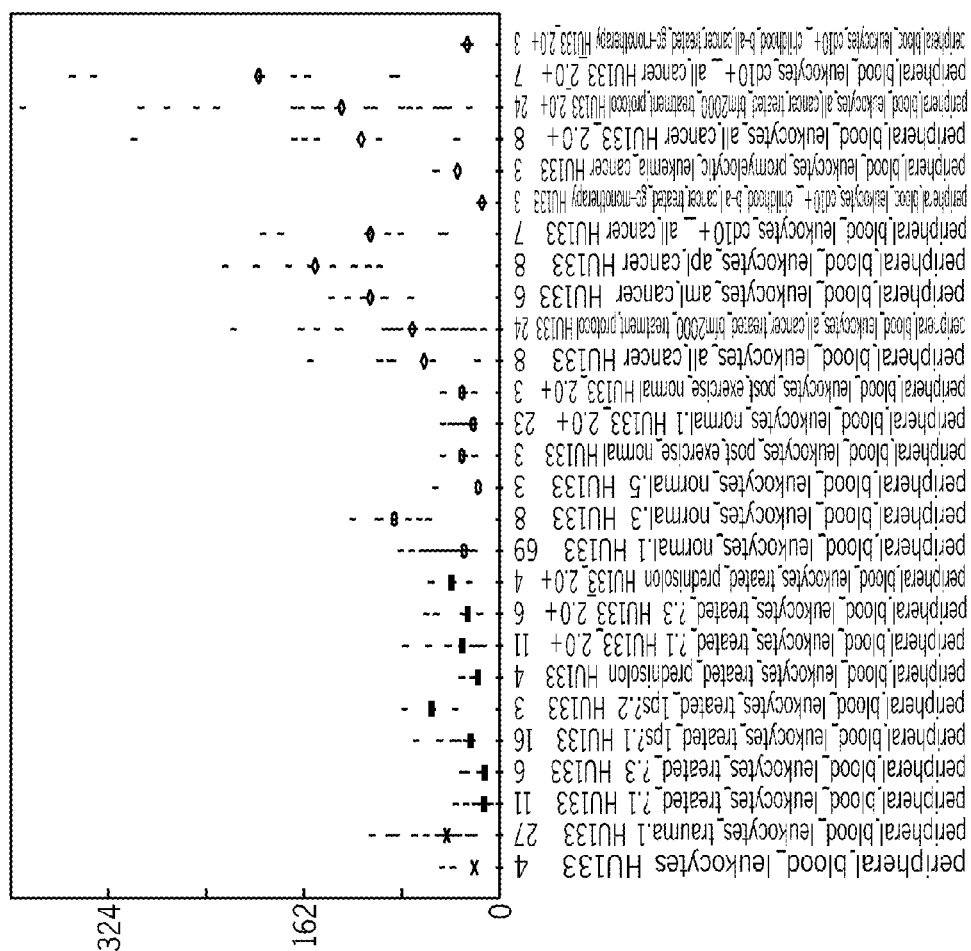
Query: 361 EEWGCHSPRSPRGWDQEPAREQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPTSNG 420
EEWGCHSPRSPRGWDQEPAREQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPTSNG
Sbjct: 390 EEWGCHSPRSPRGWDQEPAREQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPTSNG 449

Query: 421 GRSRAYMPRSRSDLDYDQDDSRDFPRSRDPHYDDFRSRERPPADPRSHHHRTRDPRDN 480
GRSRAYMPRSRSDLDYDQDDSRDFPRSRDPHYDDFRSRERPPADPRSHHHRTRDPRDN
Sbjct: 450 GRSRAYMPRSRSDLDYDQDDSRDFPRSRDPHYDDFRSRERPPADPRSHHHRTRDPRDN 509

Query: 481 GSRSGDLPYDGRLLLEEAVRKKGSEERRRPHKEEEEAYYPAPPPYSETDSQASRERRLK 540
GSRSGDLPYDGRLLLEEAVRKKGSEERRRPHKEEEEAYYPAPPPYSETDSQASRERRLK
Sbjct: 510 GSRSGDLPYDGRLLLEEAVRKKGSEERRRPHKEEEEAYYPAPPPYSETDSQASRERRLK 569

Query: 541 KNLALSRESLVV 552
KNLALSRESLVV
Sbjct: 570 KNLALSRESLVV 581

FIG. 2G-2(2)



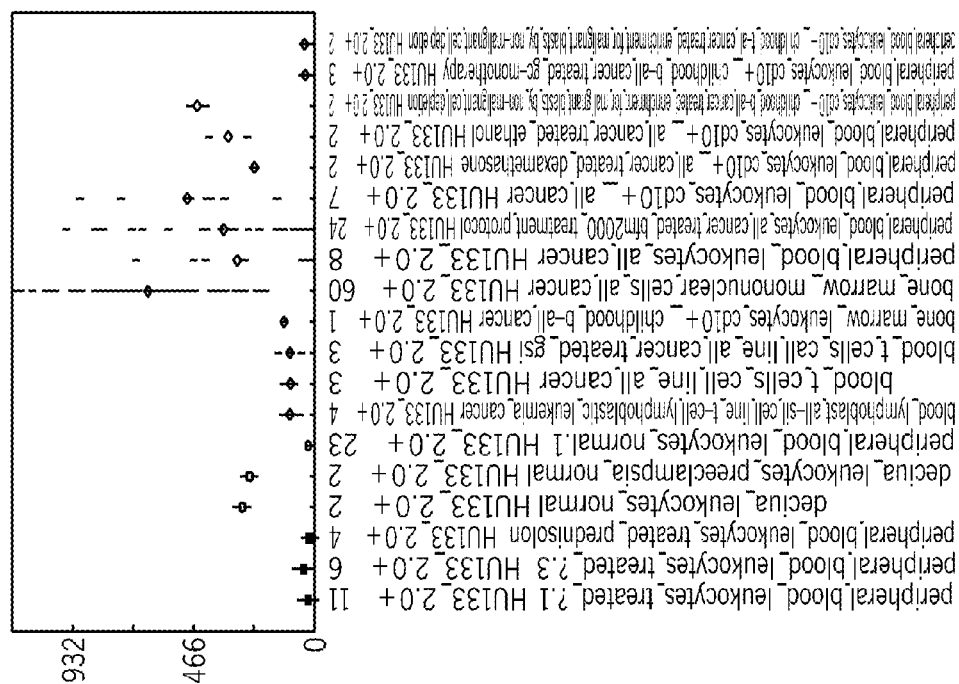
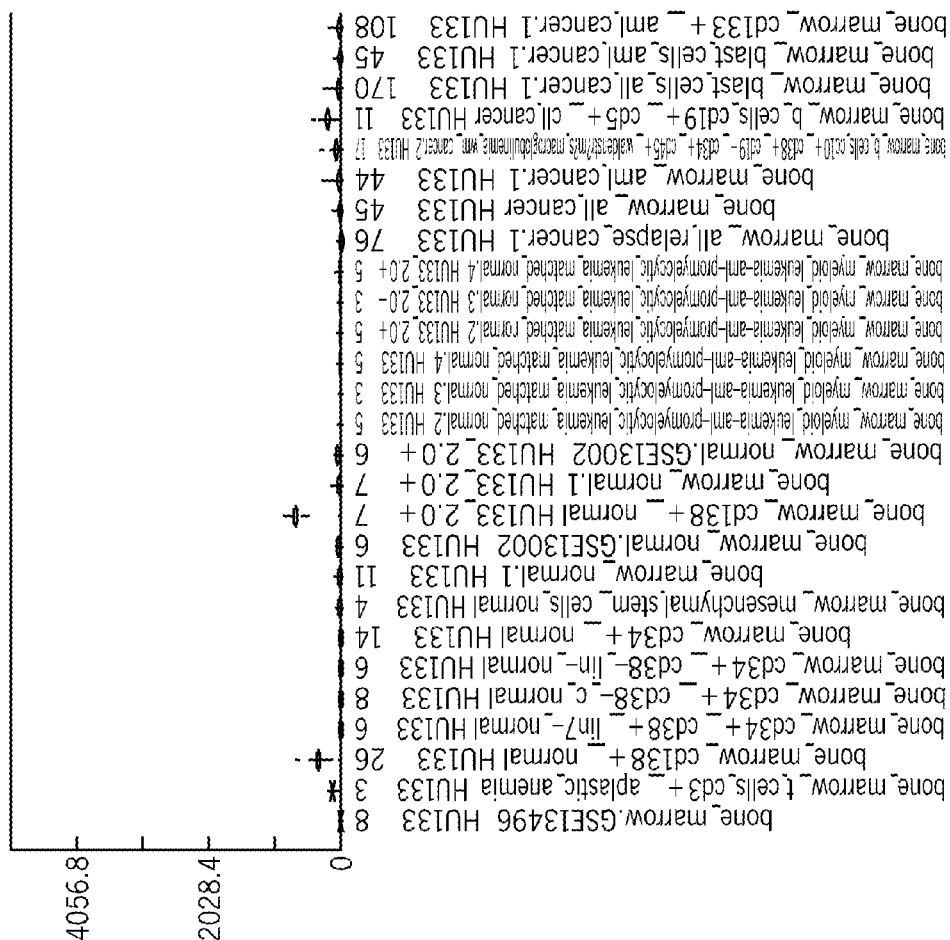
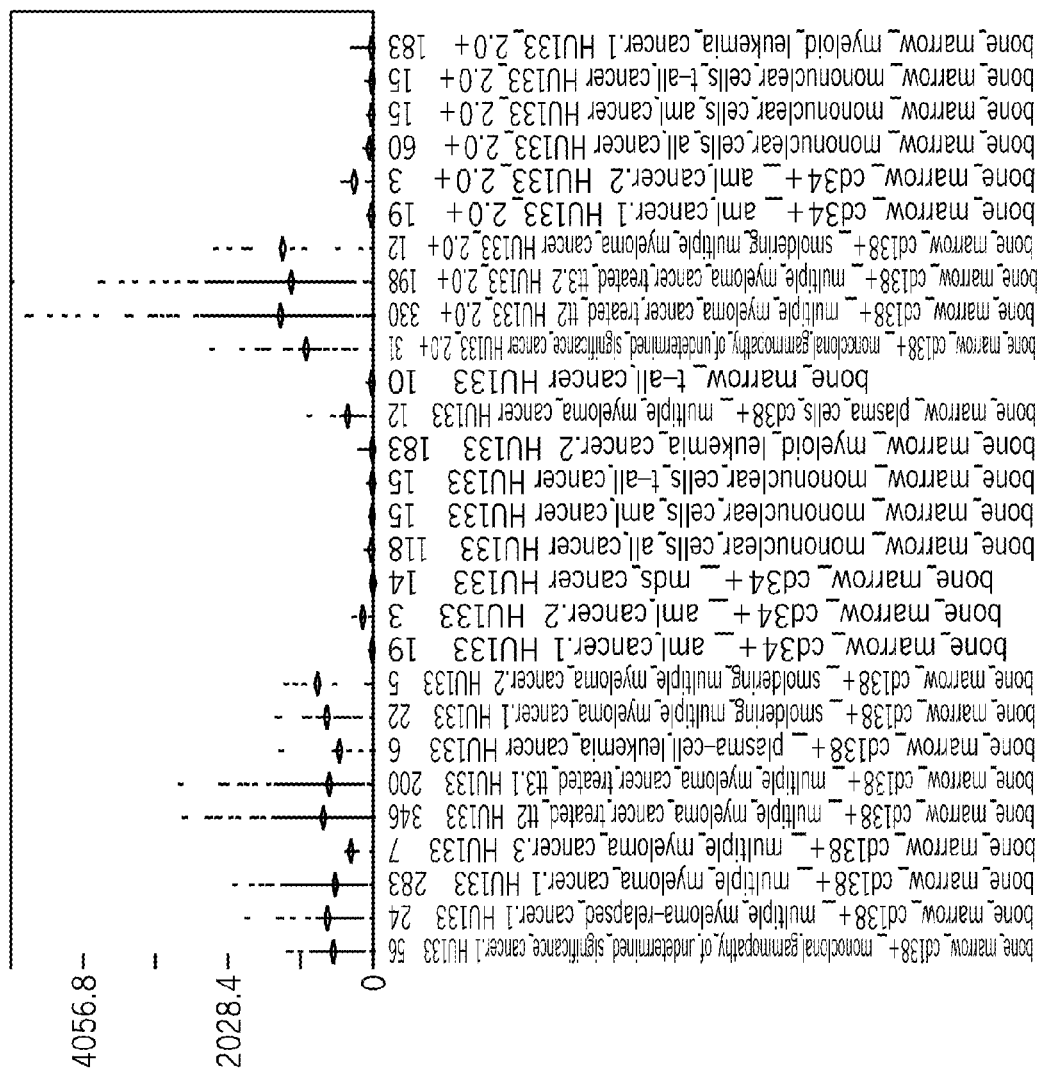
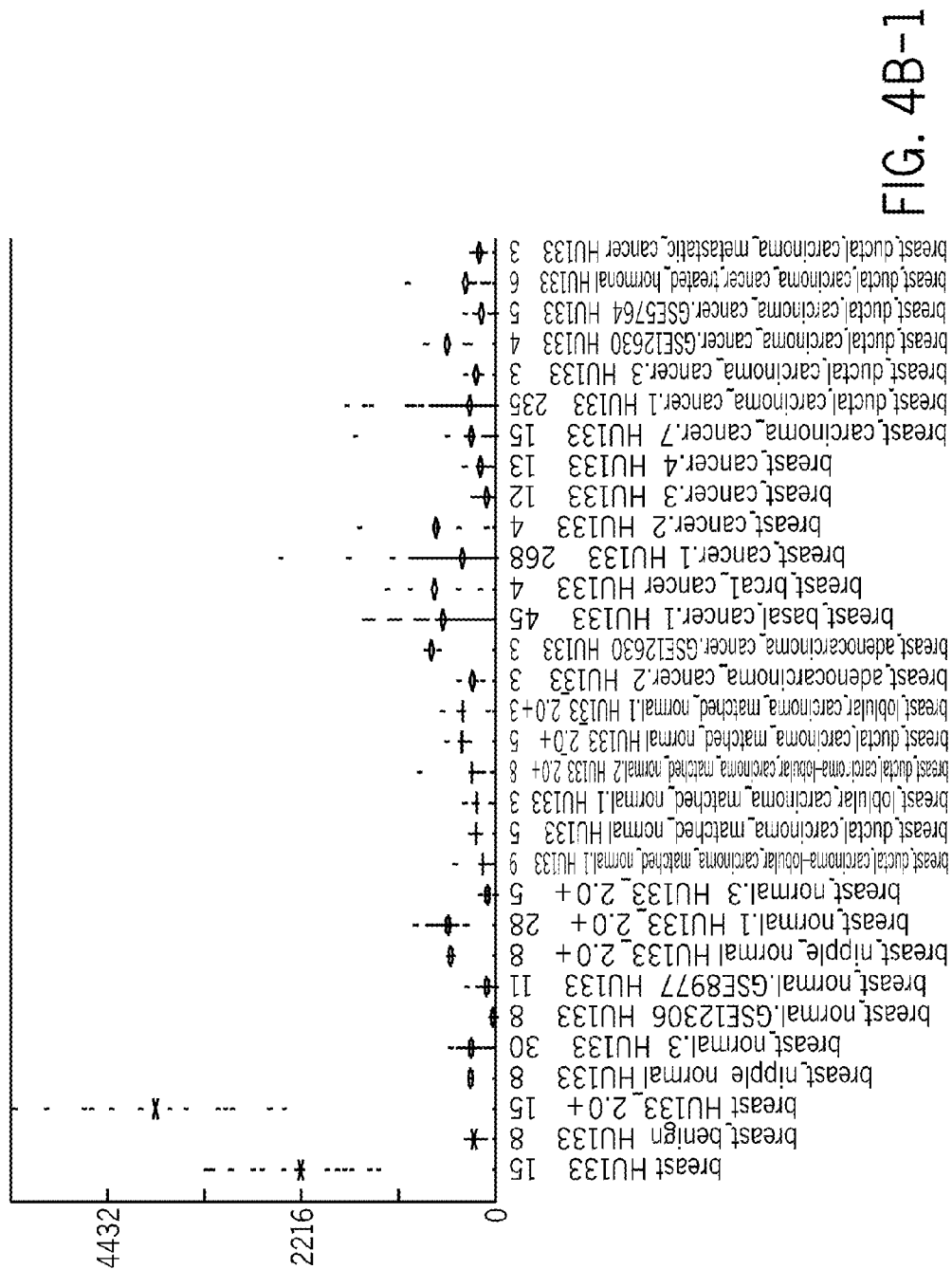


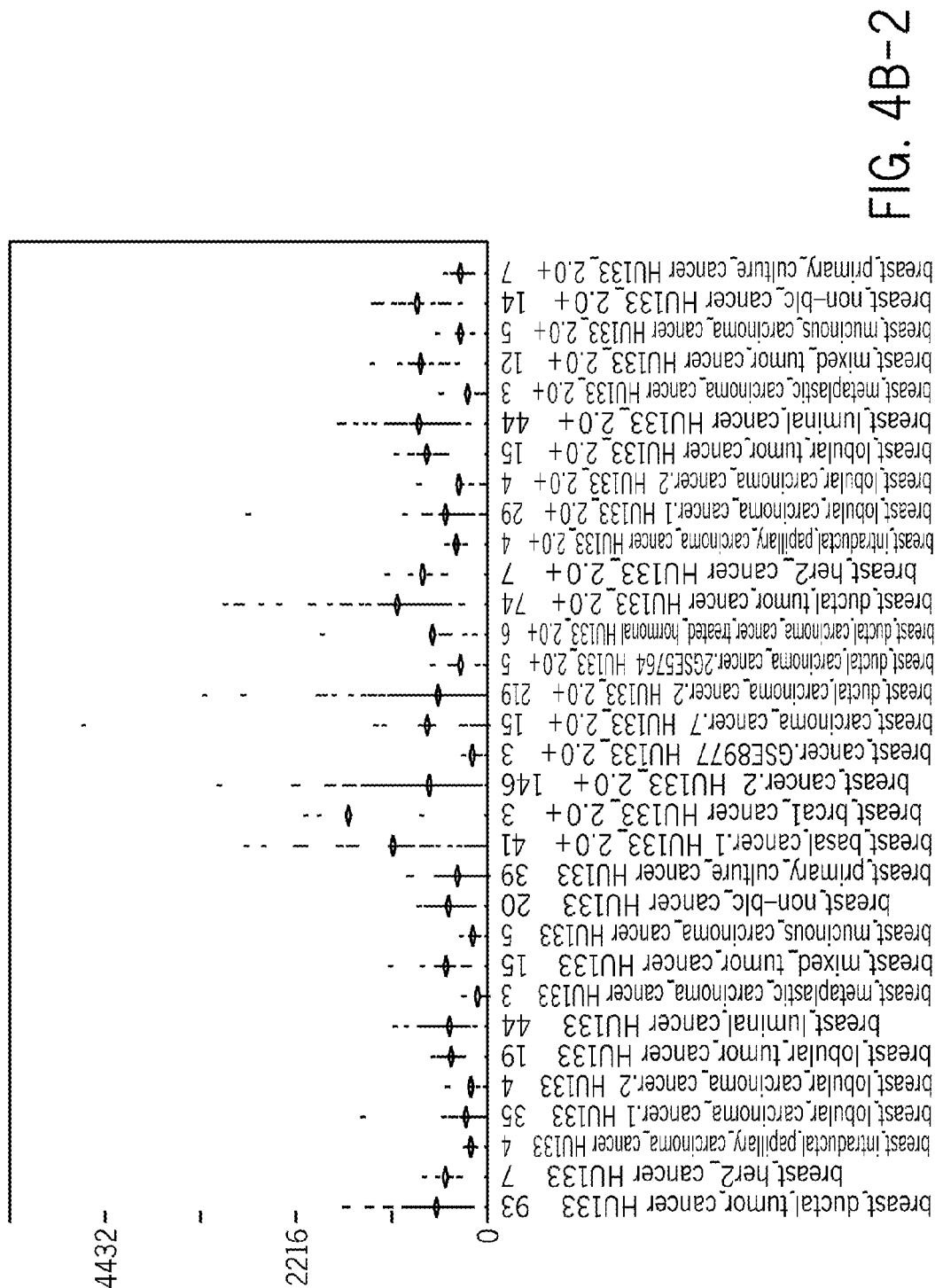
FIG. 3B

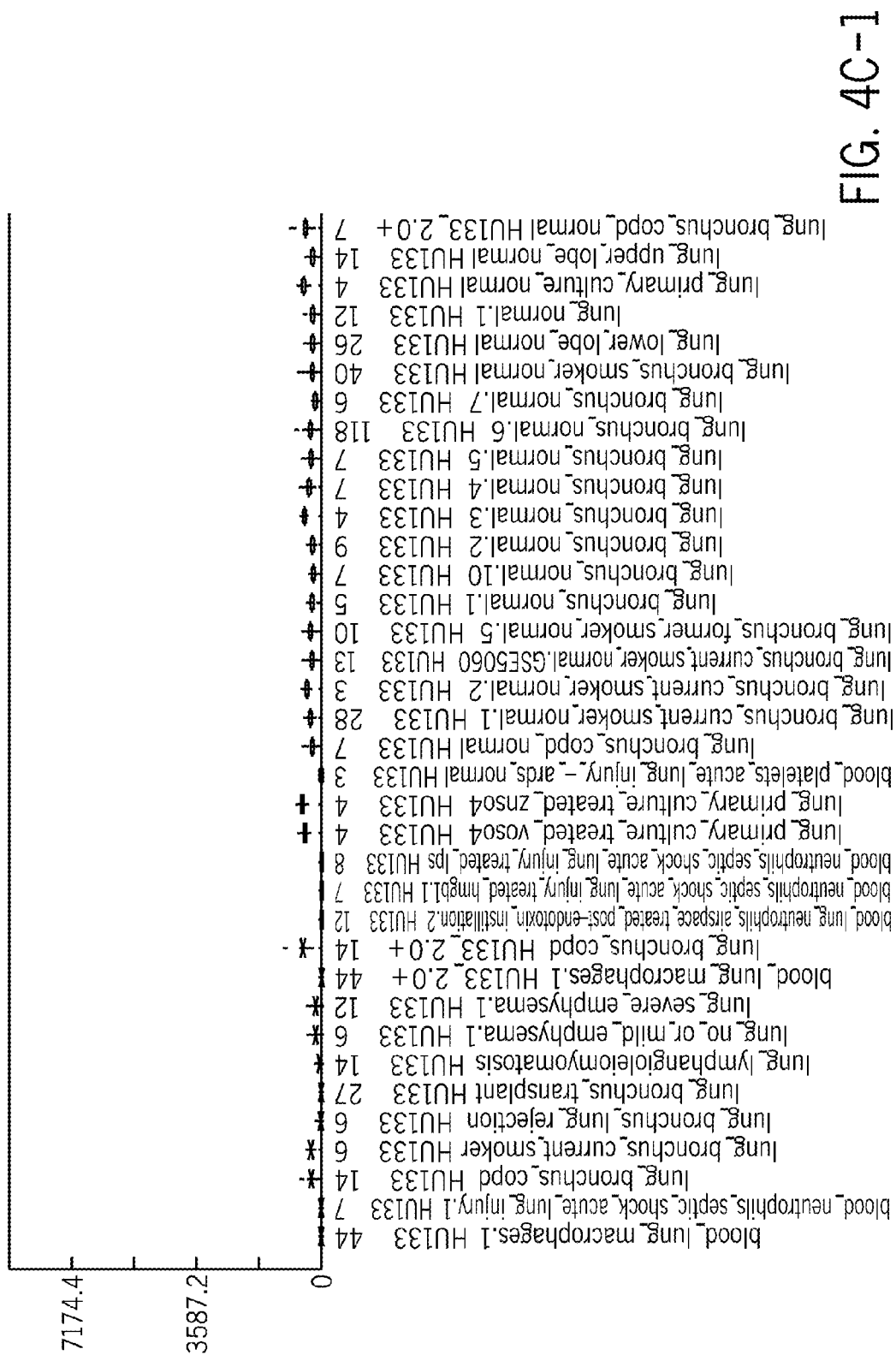
FIG. 4A-1

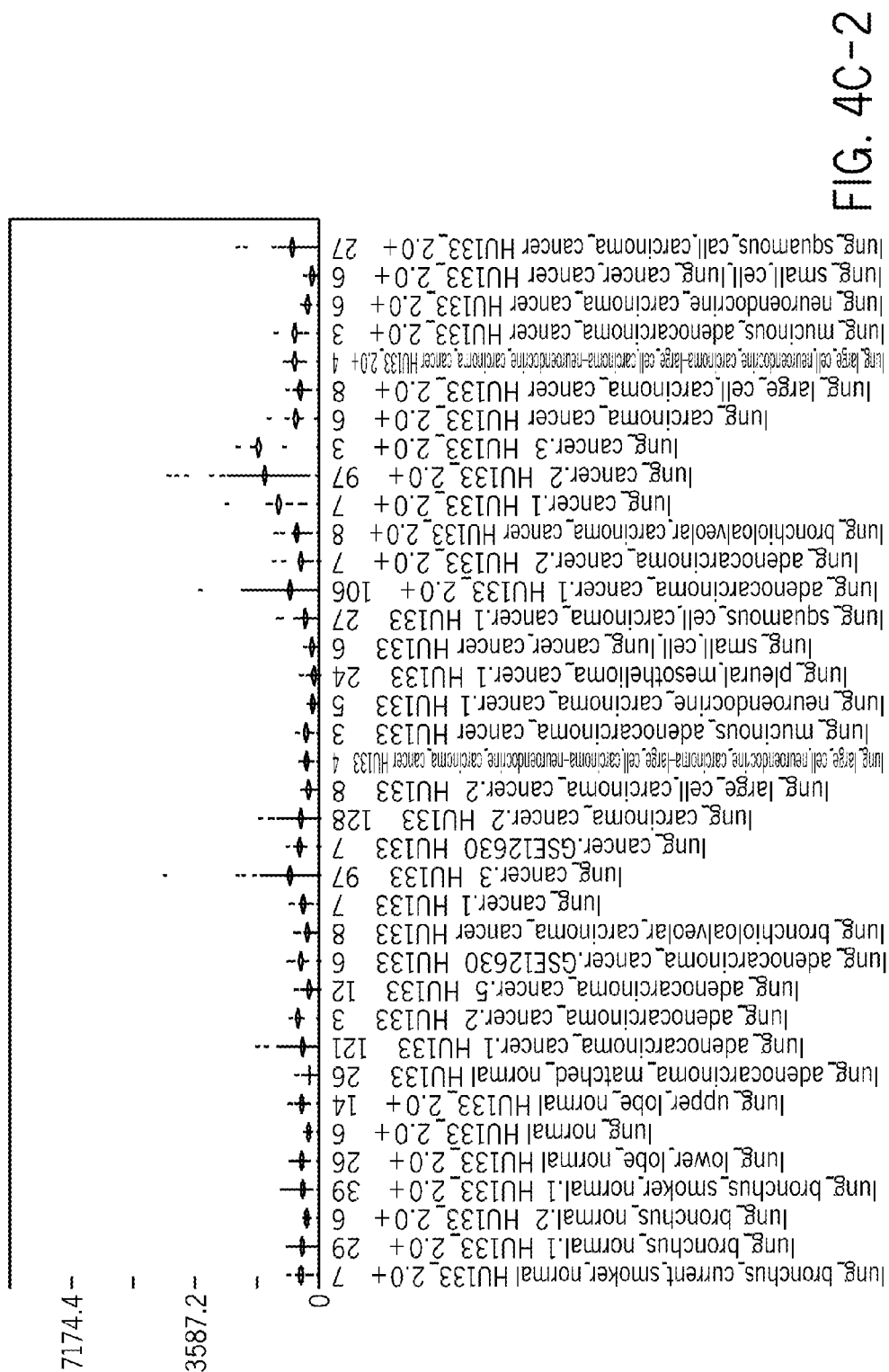


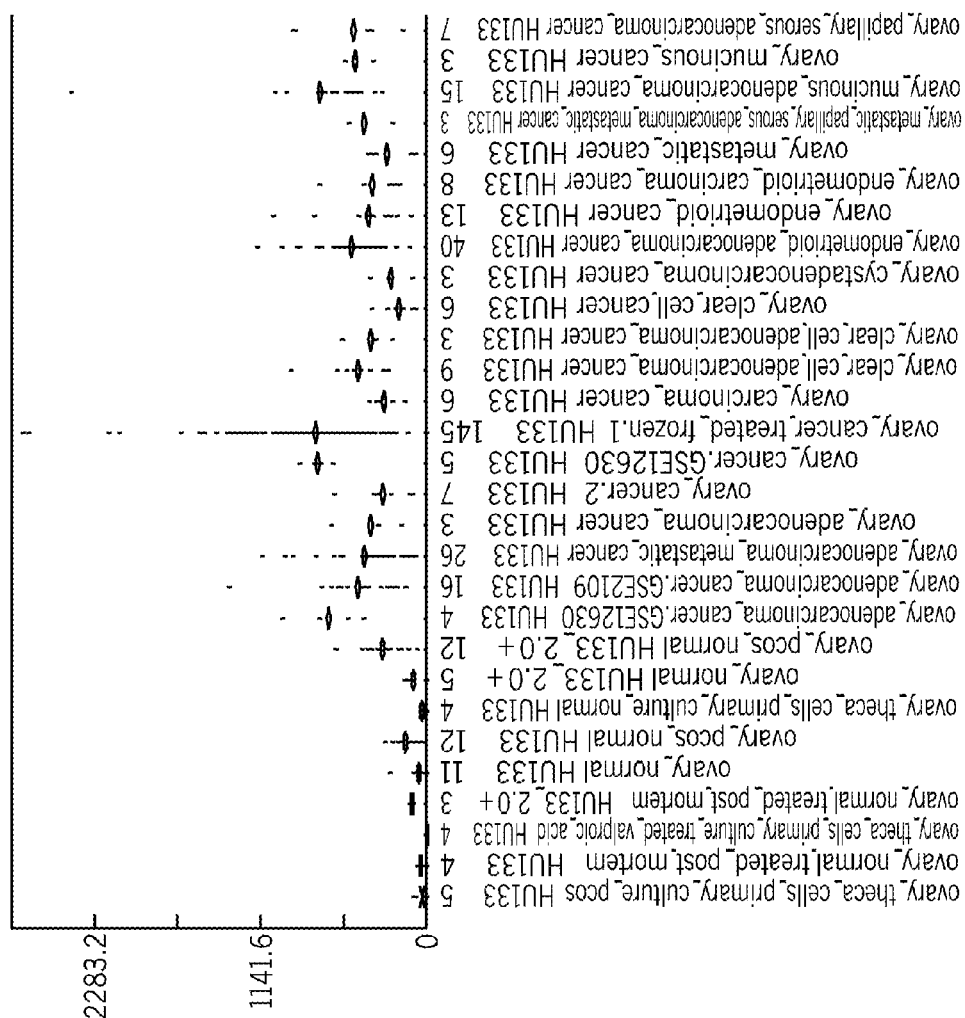


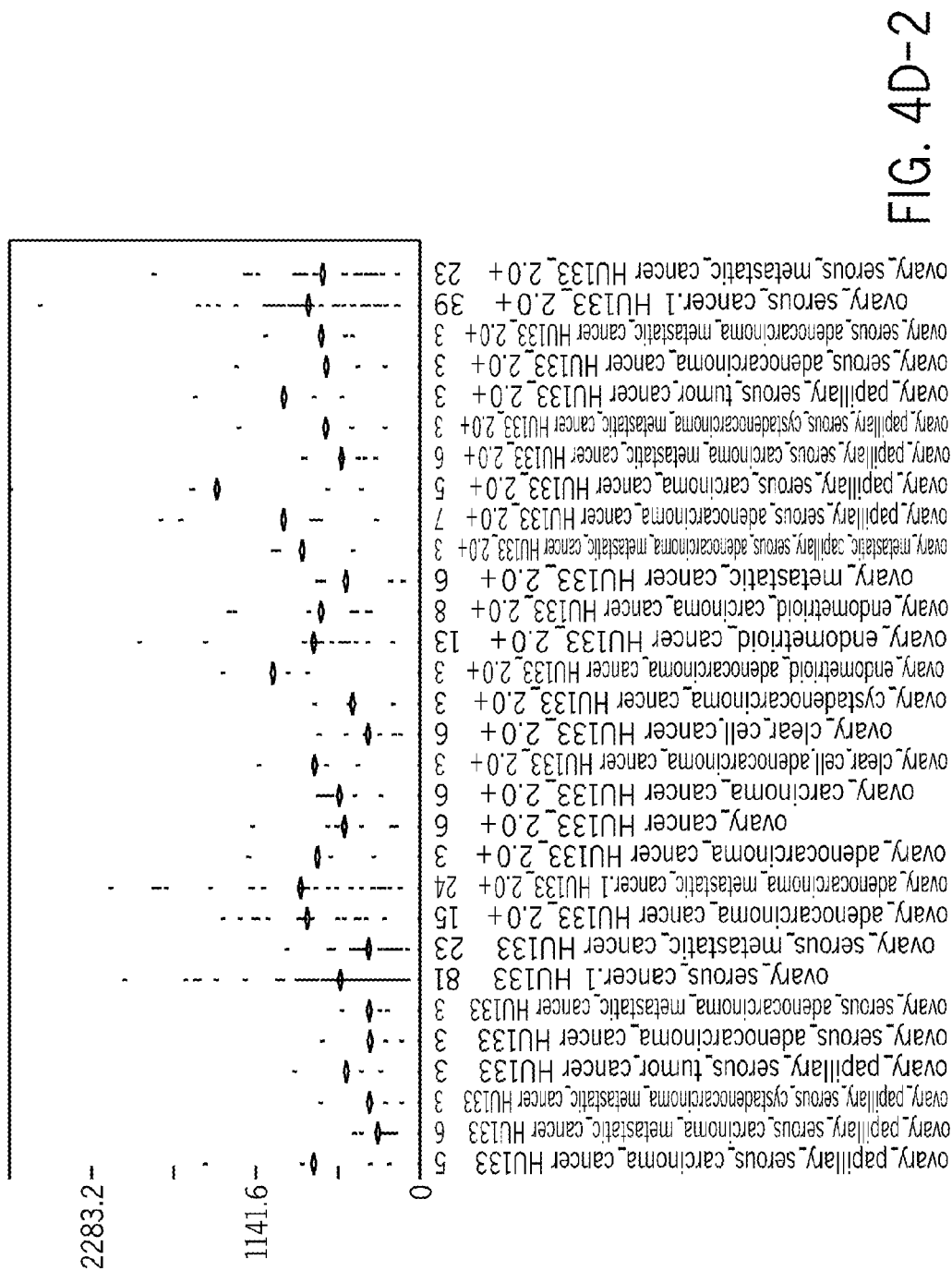


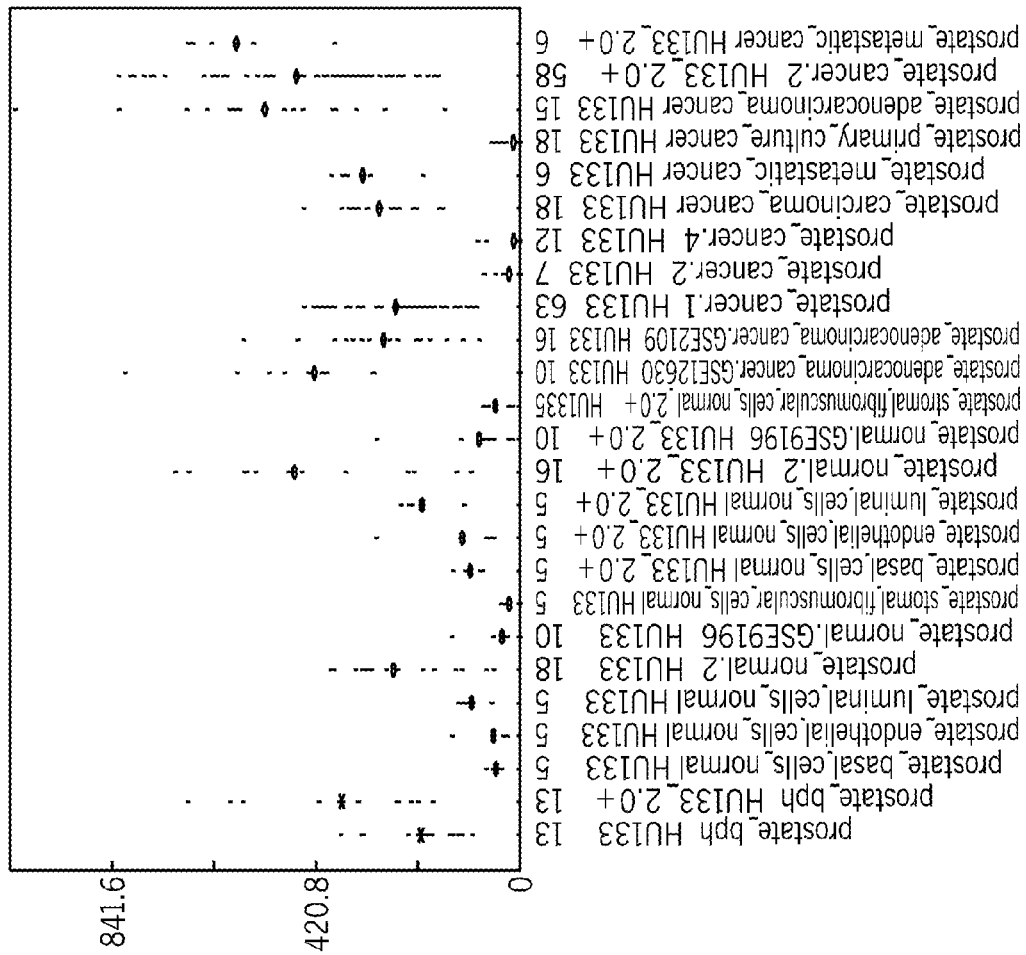












LYG6F human x mouse amino acid sequence comparison

Identities = 197/300 (65%), Positives = 230/300 (76%), Gaps = 3/300 (1%)

```
Query 1  MAVLFLLLFLCGTPQA-ADNMQAIYVALGEAVELPCPSPPTLHGDEHLSWFCSPAAGSFT 59
          MAV+ LLFLCG QA AD++Q IYVA GE+VE+PCPSPP+L G + L+WF SP AGS T
Sbjct 1  MAVVVFLLLFLCGHSQAVADSIQTIYVASGESVEMPCPSPPSLLGGQLLTWFRSPVAGSST 60

Query 60  TLVAQVQVGRPADPGKPGRESRLRLGNYSWLWLEGSKEEDAGRYWCAVLGQHNNYQNR 119
          LVAQVQV +P D KP +SR +L GNYSWLWLEGS++EDAGRYWC V+ Q+H YQNR
Sbjct 61  ILVAQVQVDKPVSDLRKPEPDSRYKLFGNYSWLWLEGSRDEDAGRYWCTVMDQNHKYQNR 120

Query 120  VYDVLVLKGSQLSARAADGSPCNVLLCSVVPSRRMDSVTWQEGKGPVRGRVQSFWGSEAA 179
          VYDV VLKGSQ S ++ DG C LLCVVVP+RR+DSVTW EG+ VRG Q FWG AA
Sbjct 121  VYDVSVLKGSQFSVKSPDGPSCAALLCSVVPARRLDSVTWLEGRNTVRGHAQYFWGEGAA 180

Query 180  LLLVCPGEGELSEPRRRPRIIRCLMTHNKGVSFSL-AASIDASPALCAPSTGWDMPWILM 238
          LLLVCP EGL E R+RRPR IRCL+ NK SFSL AAS + SP +CA WD+PWIL+
Sbjct 181  LLLVCPTEGLPETRARRPRNIRCLLPQNKRFSLAAASAEPSTVCATLPSWDVPWILV 240

Query 239  LLLTMGQGVVILALSIVLW-RQVRVGAPGRDASIPQFKPEIQYENIHLARLGPPAHKPR 297
          LL T GQGV I+ALSIVLW R+R +G+ R+ S+P FKPE+QYENIHLARL PP HK R
Sbjct 241  LLFTAGQGVTTIALSIVLWRRRRRAQGSRDREPSVPHFKEVQYENIHLARLSPPNHKTR 300
```

FIG. 5A

VSI10 human x mouse amino acid sequence comparison

Identities = 365/559 (65%), Positives = 429/559 (76%), Gaps = 34/559 (6%)

```
Query 11 RVLVCLGALLAGWVAVGL-----EAVVIGEVHENVTLH 43
          RVL+CLGALLA + GL EAV IGEVH+NVTL
Sbjct 5 RVLCLGALLARQGSAGLQLLLNPSTRANLSVRPNSEVLPGIHPDLEAVAIGEVHNDVTLR 64

Query 44 CGNISGLRGQVTWYRNNSEPVFLLSSNSSLRPAEPRFSLVDATSLHIESLSLGDEGIYTC 103
          CG+ SG RG VTWYRN+SEP FL+S NSSL PA PRFSL DA +L IE+L L D+G YTC
Sbjct 65 CGSASGSRGLVTWYRNDSEPAFLVSFNSSLPPAAPRFSLEDAGALRIEALREDDGNYTC 124

Query 104 QEILNVTQWFQVWLQVASGPYQIEVHVIVATGTLPNGTLYAARGSQVDFSCNSSSRPPPVV 163
          QE+LN T WF V L+VASGP +EV+I ATGTLPNGTLYAARGSQVDF+C S+++PPP V
Sbjct 125 QEVLNETHWFPVRLRVASGPAYVEVNISATGTLPNGTLYAARGSQVDFNCCSAAQPPPEV 184

Query 164 EWWFQALNSSSESFGHNLTVNFFSLLLISPNIQNYTCLALNQLSKRHRKVTTELLVYYP 223
          EWW Q +S E G NL+ N F+L+L+S NLQGYTC A N LS R RKVTTELLVY+P
Sbjct 185 EWWIQT-HSIPEFLGKNLSANSFTLMLMSQNLQGYTC SATNVLSGRQRKVTTELLVYWP 243
```

FIG. 5B-1

Query 224 PPSAPQCWAQMASGSFMLQLTCRWDGGYPDPDFLWIEEPGGVIVGKSKLGVEMLSQSLS 283
PPSAPQC +++S S L+L C WDGYPDP FLW EEPGG I+G SKL + LS +QL
Sbjct 244 PPSAPQCSVEVSSESTTLELACNWDGGYPDPFLWTEEPGGTIMGNSKL--QTLSPAQLL 301

Query 284 DGKKFKCVTSHIVGPESGASCMVQIRGPSLLSEPMKTCFTGGNVTLTCQVSGAYPPAKIL 343
+GKKFKCV +HI+GPESGASC+V++ P L S+PM+TCF GGNVTLTC+VSGA PPA+I
Sbjct 302 EGKKFKCVGNHILGPESGASCVVKLSSPLLPSQPMRTCFVGGNVTLTCEVSGANPPARIQ 361

Query 344 WLRNLTQPEVLIQPSRHLITQDQNSTLTIHNCSQDLDEGYICRADSPVGVREMEIWL 403
WLRNLTQP IQPSS ++ITQ GQ+S+LTIHNCSQDLDEG+Y C+A++ VGVR IWL
Sbjct 362 WLRNLTQPA--IQPSSHYIITQQGQSSSLTIHNCSQDLDEGFYICQAENLVGVRATNIWL 419

Query 404 SVKEPLNIGGIVGTIVSLLLLGLAIISGLLLHYSVPFCWKVGNTSRGQNMDDVMVLVDS- 462
SVKEPLNIGGIVGT+VSLLLLGLA++SGL L+YSP F WK G+T RCQ+M DVMVLVDS
Sbjct 420 SVKEPLNIGGIVGTIVSLLLLGLAVVSGLTLYSPAFWWKGGSTFRGQDMGDVMVLVDSE 479

Query 463 -EEEEEEEEEEEDAAGVEQEGAREREELPKETPKQDHIHRVTALVNGNIEQMNGFQDL 521
EEEEEEEEEE+ED A ++ E EELPK I K HIHRVTALVNGN+++MGNGFQ+
Sbjct 480 EEEEEEEEEEEKEDVAEEVEQETNETEELPKGISKHGHIHRVTALVNGNLD RMGNGFQEF 539

Query 522 QDDSSSEQSDIVQEEDRPV 540
QDDS +QS IVQE+ +PV
Sbjct 540 QDDSDGQQSGIVQEDGKPV 558

FIG. 5B-2

LSR human x mouse (ref|NP_059101.1) amino acid sequence comparison

Identities = 467/592 (79%), Positives = 496/592 (84%), Gaps = 15/592 (2%)

```
Query 62  SHPAAAGRDVVFVWLLSTWCTAPARAIQVTVSNPYHVVLFPVTLPCITYQMTSTPTQ 121
          SHPA      +FV L L +C  A AIQVTV +PYHVVLFPVTL CTYQM++T T
Sbjct 14  SHPAT-----TIFVCLFLIIYCPDRASAIQVTVDPYPYHVVLFPVTLHCTYQMSNTLTA 68

Query 122 PIVIWKYKSECRDRIADAFSPASVDNQLNAQLAAGNPGYNPYVEQCDSVRTVRVVKQKQ 181
          PIVIWKYKSECRDR+ADAFSPASVDNQLNAQLAAGNPGYNPYVEQCDSVRTVRVVKQKQ
Sbjct 69  PIVIWKYKSECRDRVADAFSPASVDNQLNAQLAAGNPGYNPYVEQCDSVRTVRVVKQKQ 128

Query 182 NAVTLGDYYQGRITITGNADLTFTDQTAWGDSGVYYCSVVSQAQDLQGNNEAYAEILVLGR 241
          NAVTLGDYYQGRITITGNADLTFT+QTAWGDSGVYYCSVVSQAQDL GNNEAYAEILVLGR
Sbjct 129 NAVTLGDYYQGRITITGNADLTFTDQTAWGDSGVYYCSVVSQAQDLQGNNEAYAEILVLGR 188

Query 242 TSGVAELLPGFQAGPIEDWLFVVVVCLAFLIFLLLGICWCQCCPHTCCCYVRCPCCPDK 301
          TS  ELLPGF+AGP+EDWLFVVVVCLA+ L FLLLGICWCQCCPHTCCCYVRCPCCPDK
Sbjct 189 TSEAPELLPGFRAGPLEDWLFVVVVCLASLLFLLLGICWCQCCPHTCCCYVRCPCCPDK 248

Query 302 CCCPEALYAAGKAATSGVPSIYAPSTYAHLSPAKTPPPAMIPMPAYNGYPGGYPGDVD 361
          CCCPEALYAAGKAATSGVPSIYAPS Y HLSPAKT      P      P GYPGD
Sbjct 249 CCCPEALYAAGKAATSGVPSIYAPSIYTHLSPAKT----PPPPAMIPMRPPYGYPGDFD 304
```

FIG. 5C-1

Query 362 RSSSAGGQGSYVPLLRDTSSVASEVRSYRIQASQQDDSMRVLYYMEKELANFDPSRPG 421
R+SS GG S VPLLR+ D SV+SEVRSYRIQA+QQDDSMRVLYYMEKELANFDPSRPG
Sbjct 305 RTSSVGGHSSQVPLLREVDGSVSSEVRSYRIQANQQDDSMRVLYYMEKELANFDPSRPG 364

Query 422 PPSGRVERAMSEVTS LHEDDWSRPSRGFALTPIRDEEWGGHSPRSPRGWDQEPAREQAG 481
PP+GRVERAMSEVTS LHEDDWSRPSR PALTPIRDEEW HSPRSPR W+QEP +EQ
Sbjct 365 PPNGRVERAMSEVTS LHEDDWSRPSRAPALTPIRDEEWNHSPRSPRTWEQEPLQEQPR 424

Query 482 GGWRARRPRARSVDALDDLTPSTAESGRSPTSNGGRSRAYMPPRSRSRDDLYDQDDSR 541
GGW + RPRARSVDALDD+ P + ESG SP S+G R RAY PPRSRSRDDLYD DD R
Sbjct 425 GGWGSGRPRARSVDALDDINRPGSTESGRSSPPSSGRRGRAYAPPRSRSRDDLYDPDDPR 484

Query 542 DFPRS RDPH-YDDFRSRERPPADPRSHHRTDPRDNGSRSGDLPYDGRLLLEEAVRKKGS 600
D P SRDPH YDD RSR+ P ADPRS R+ DPRD G RS D YDGRLLLEE++KKG+
Sbjct 485 DLPHSRDPHYDDLRSRD-PRADPRS-RQRSHDPRDAGFRSRDPQYDGRLLLEEALKKKGA 542

Query 601 ---EERRRPHKEEEEAYYPAPPYSETDSQASRERRLKKNLALSRESLVV 649
R +EEEE +YYPAPPYSETDSQASRERR+KKNLALSRESLVV
Sbjct 543 GERRRVYREEEEEEGHYPPAPPYSETDSQASRERRMKNLALSRESLVV 594

FIG. 5C-2

LSR human x mouse (ref| NP_001157656.1) amino acid sequence comparison

Identities = 453/592 (77%), Positives = 480/592 (82%), Gaps = 34/592 (5%)

```
Query 62 SHPAAAGRDVVFVWLLLSTWCTAPARAIQVTVSNPYHVILFQPVTLPCITYQMTSTPTQ 121
        SHPA      +FV L L +C A AIQVTV +PYHVILFQPVTL CTYQM++T T
Sbjct 14 SHPAT-----TIFVCLFLIIYCPDRASAIQVTVDPYHVILFQPVTLHCTYQMSNTLTA 68

Query 122 PIVIWKYKSFCRDRIADAFSPASVDNQLNAQLAAGNPGYNPYVEQCDSVRTVRVVATKQG 181
        PIVIWKYKSFCRDR+ADAFSPASVDNQLNAQLAAGNPGYNPYVEQCDSVRTVRVVATKQG
Sbjct 69 PIVIWKYKSFCRDRVADAFSPASVDNQLNAQLAAGNPGYNPYVEQCDSVRTVRVVATKQG 128

Query 182 NAVTLGDYYQGRRITITGNADLTFDQTAWGDSGVYYCSVVSAQDLQGNNEAYAEILIVLGR 241
        NAVTLGDYYQGRRITITGNADLTF+QTAWGDSGVYYCSVVSAQDL GNNEAYAEILIVL
Sbjct 129 NAVTLGDYYQGRRITITGNADLTFFQTAWGDSGVYYCSVVSAQDLQGNNEAYAEILIVL -- 186

Query 242 TSGVAELLPGFQAGPIEDWLFVVVVCLAAFLIFLLLGICWCQCCPHTCCCYVRCPCCPDK 301
        DWLFVVVVCLA+ L FLLLGICWCQCCPHTCCCYVRCPCCPDK
Sbjct 187 -----DWLFVVVVCLASLLFFLLLGICWCQCCPHTCCCYVRCPCCPDK 229

Query 302 CCCPEALYAAGKAATSGVPSIYAPSTYAHLSPAKTPPPPAMIPMGPAYNGYPGGYPGDVD 361
        CCCPEALYAAGKAATSGVPSIYAPS Y HLSPAKT P P GYPGD D
Sbjct 230 CCCPEALYAAGKAATSGVPSIYAPSIYTHLSPAKT-----PPPPPAMIPMRPPYGYPGDFFD 285
```

FIG. 5C-3

Query 362 RSSSAGGQGSYVPLLRTDSSVASEVRSGYRIQASQQDDSMRVLYYMEKELANFDPSRPG 421
R+SS GG S VPLL R+ D SV+SEVRSGYRIQA+QQDDSMRVLYYMEKELANFDPSRPG
Sbjct 286 RTSSVGGHSSQVPLLREVDGSVSSEVRSGYRIQANQQDDSMRVLYYMEKELANFDPSRPG 345

Query 422 PPSCRVERAMSEVTS LHEDDWR SRPSRG PALTPIRDEEWGGHSPRSPRGWDQEPAREQAG 481
PP+GRVERAMSEVTS LHEDDWR SRPSR PALTPIRDEEW HSPRSPR W+QEP +EQ
Sbjct 346 PPNGRVERAMSEVTS LHEDDWR SRAPALTPIRDEEWNRHSPRSPRTWEQEPLQEQQPR 405

Query 482 GGWRARRPRARSVDALDDLTPPSTAESGSRSPSTNGGRSRAYMPPRSRSDDLYDQDDSR 541
GGW + RPRARSVDALDD+ P + ESG SP S+G R RAY PPRSRSRDDLYD DD R
Sbjct 406 GGWGSGRPRARSVDALDDINRPGSTESGRSSPSSGRRGRAYAPPRSRSRDDLYDPDDPR 465

Query 542 DFPRSRDPH-YDDFRSRERPPADPRSHHRTDPRDNGSRSGDLPYDGRLLLEEAVRKKGS 600
D P SRDPH YDD RSR+ P ADPRS R+ DPRD G RS D YDGRLLEEA++KKG+
Sbjct 466 DLPHSRDPHYDDLRSRD-PRADPRS-RQRSHDPRDAGFRSRDPQYDGRLLLEEALKKKGA 523

Query 601 ---EERRRPHKEEEEEAYPPAPPPYSETDSQASRERRLKKNLALSRESLVV 649
R +EEEE +YPPAPPPYSETDSQASRERR+KKNLALSRESLVV
Sbjct 524 GERRRVYEEEEEEEGHYPPAPPPYSETDSQASRERMKNLALSRESLVV 575

FIG. 5C-4

TMEM25 human x mouse (ref: cd4109) amino acid sequence comparison

```
Query 1 MALPPGPAALRHTLLLLPALLSSGNGELEPQIDGQTWAERALRENERHAFTCRVAGGPGT 60
      M LP A LRHTLLLLPALLSSG GEL PQIDGQTWAERALRENE HAFTCRVAGG T
Sbjct 1 MELPLSQATLRHTLLLLPALLSSGQGELAPQIDGQTWAERALRENEHHAFTCRVAGGSAT 60

Query 61 PRLAWYLDGQLQEASTSRLLSVGGGEAFSGGTSTFTVTAHRAQHELNCSLQDPRSGRSANA 120
      PRLAWYLDGQLQEA+TSRLLSVGG+AFSGGTSTFTVTA R+QHELNCSLQDP SGR ANA
Sbjct 61 PRLAWYLDGQLQEATTSRLLSVGGDAFSGGTSTFTVTAQRSQHELNCSLQDPGSGRPANA 120

Query 121 SVILNVQFKPEIAQVGAKYQEAQGPGLLVVLFALVRANPPANVTWIDQDGPVTVNTSDFL 180
      SVILNVQFKPEIAQVGAKYQEAQGPGLLVVLFALVRANPPANVTWIDQDGPVTVN SDFL
Sbjct 121 SVILNVQFKPEIAQVGAKYQEAQGPGLLVVLFALVRANPPANVTWIDQDGPVTVNASDFL 180

Query 181 VLDAQNYPWLTNHTVQLQLRSLAHNLSVVATNDVGVTASLAPAGLLATRVEVPLLGIWV 240
      VLDAQNYPWLTNHTVQLQLRSLAHNLSVVATNDVGVTASLAPAGLLATR+EVPLLGIWV
Sbjct 181 VLDAQNYPWLTNHTVQLQLRSLAHNLSVVATNDVGVTASLAPAGLLATRIEVPLLGIWV 240

Query 241 AAGLALGTLVGFTSLVACLVCRKKEKTKGPSRHPSLISSDSNNLKLNNVRLPRENMSLPS 300
      A GLALGTLVGFTSLVACLVCRKKEKTKGPSR PS LISSDSNNLKLNNVRLPRENMSLPS
Sbjct 241 AGGLALGTLVGFTSLVACLVCRKKEKTKGPSRRPSLISSDSNNLKLNNVRLPRENMSLPS 300

Query 301 NLQLNDLTPDSRAVKPADRCMAQNNSRPELLDPEPGGLLTSQGFIRLPVLGYIYRVSSVS 360
      NLQLNDLTPD R K +R MAQ++SRPELL+ EPGGLLTS+GFIRLP+LGYIYRVSSVS
Sbjct 301 NLQLNDLTPDLRG-KATERPMAQHSSRPELLEAEPGGLLTSRGFIRLPMLGYIYRVSSVS 359

Query 361 SDEIWL 366
      SDEIWL
Sbjct 360 SDEIWL 365
```

FIG. 5D

SEQ ID NO:	Primer ID	Primer sequence	Restriction site
51	100-690	GAGAACTTGGCAGGCTCTCC	-
52	100-691	CACACTTCCCAGCAGATGTC	-
53	100-729	CTA GCTAGC <u>CACC</u> ATGGCAGTC TTATTCCTCCTC	NheI
54	100-730	CGC GAATTC GCCTGGGCTTGTG GGCAGGTG	EcoRI

FIG. 6

G6F_EGFP ORF nucleotide sequence in pIRESpuro vector

ATGGCAGTCTTATTCTCCTCCTGTTCTATGTGGAAC TCCCAGGCTGCAGACAACATG
CAGGCCATCTATGTGGCCTTGGGGGAGGCAGTAGAGCTGCCATGTCCCTCACCACCTACT
CTACATGGGGACGAACACCTGTCATGGTTCTGCAGCCCTGCAGCAGGCTCCTTCACCACC
CTGGTAGCCCAAGTCCAAGTGGGCAGGCCAGCCCCAGACCCTGGAAAAC CAGGAAGGGAA
TCCAGGCTCAGACTGCTGGGGAAC TATTCTTTGTGGTTGGAGGGATCCAAAGAGGAAGAT
GCCGGGCGGTACTGGTGCGCTGTGCTAGGTCAGCACCACAAC TACCAGAACTGGAGGGTG
TACGACGTCTTGGTGCTCAAAGGATCCCAGTTATCTGCAAGGGCTGCAGATGGATCCCCC
TGCAATGTCTCCTGTGCTCTGTGGTCCCCAGCAGACGCATGGACTCTGTGACCTGGCAG
GAAGGGAAGGGTCCCGTGAGGGGCGGTTCAGTCCTTCTGGGGCAGTGAGGCTGCCCTG
CTCTTGGTGTGCTCTGGGGAGGGGCTTCTGAGCCCAGGAGCCGAAGACCAAGAATCATC
CGCTGCCTCATGACTCACAACAAAGGGGT CAGCTTTAGCCTGGCAGCCTCCATCGATGCT
TCTCCTGCCCTCTGTGCCCTTCCACGGGCTGGGACATGCCTTGGATTCTGATGCTGCTG
CTCACAATGGGCCAGGGAGTTGTCATCCTGGCCCTCAGCATCGTGCTCTGGAGGCAGAGG
GTCCGTGGGGCTCCAGGCAGAGATGCCTCGATTCTCAGTTCAAACCCGAAATCCAGGTC
TATGAGAACATCCATTTGGCCCGTCTTGCCCACTGCCACAAGCCCAGGCGAATTCTG

FIG. 7-1

CAGTCGACGGTACCGCGGGCCCGGGATCCACCGGTCGCCACCATGGTGAGCAAGGGCGAG
GAGCTGTTACCGGGGTGGTGGCCATCCTGGTCGAGCTGGACGGCGACGTAAACGGCCAC
AAGTTCAGCGTGTCGGCGAGGGCGAGGGCGATGCCACCTACGGCAAGCTGACCCTGAAG
TTCATCTGCACCACCGCAAGCTGCCCCTGCCCTGGCCCACCCTCGTGACCACCCTGACC
TACGGCGTGCACTGCTTCAGCCGCTACCCCGACCACATGAAGCAGCACGACTTCTTCAAG
TCCGCCATGCCCCAAGGCTACGTCCAGGAGCGCACCATCTTCTTCAAGGACGACGGCAAC
TACAAGACCCGCGCCGAGGTGAAGTTCGAGGGCGACACCCTGGTGAACCGCATCGAGCTG
AAGGGCATCGACTTCAAGGAGGACGGCAACATCCTGGGGCACAAGCTGGAGTACAACTAC
AACAGCCACAACGTCTATATCATGGCCGACAAGCAGAAGAACGGCATCAAGGTGAACTTC
AAGATCCGCCACAACATCGAGGACGGCAGCGTGCAGCTCGCCGACCACTACCAGCAGAAC
ACCCCATCGGCGACGGCCCCGTGCTGCTGCCCCGACAACCACTACCTGAGCACCCAGTCC
GCCCTGAGCAAAGACCCCAACGAGAAGCGCGATCACATGGTCCTGCTGGAGTTCGTGACC
GCCGCCGGGATCACTCTCGGCATGGACGAGCTGTACAAGTAA

FIG. 7-2

G6F_EGFP ORF protein sequence in pIRESpuro vector

MAVLFLLLFLCGTPQAADNMQAIYVALGEAVELPCSPPTLHGDEHLSWFCSPAAGSFTT
LVAQVQVGRPAPDPGKPGRESRLRLLGNYSLWLEGSKEEDAGRYWCAVLGQHHNYQNWRV
YDVLVLKGSQLSARAADGSPCNVLLCSVPSRRMDSVTWQEGKGPVKGRVQSFWGSEAAL
LLVCPGEGLEPRSRRPRIIRCLMTHNKGVSFSLAASIDASPALCAPSTGWDMPWILMLL
LTMGQGQVVILALSIVLWRQVRGAPGRDASIPQFKPEIQVYENIHLARLGPPAHKPRRIL
QSTVPRARDPPVATMVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLT
LICTTGKLPVPWPTLVTTLTYGVQCFSRYPDHMKQHDFFKSAMPEGYVQERTIFFKDDGN
YKTRAEVKFEGDTLVNRIELKGIDFKEDGNILGHKLEYNNSHNVYIMADKQKNGIKVNF
KIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSTQSALSKDPNEKRDHMLLEFVT
AAGITLGMDELYK

FIG. 8

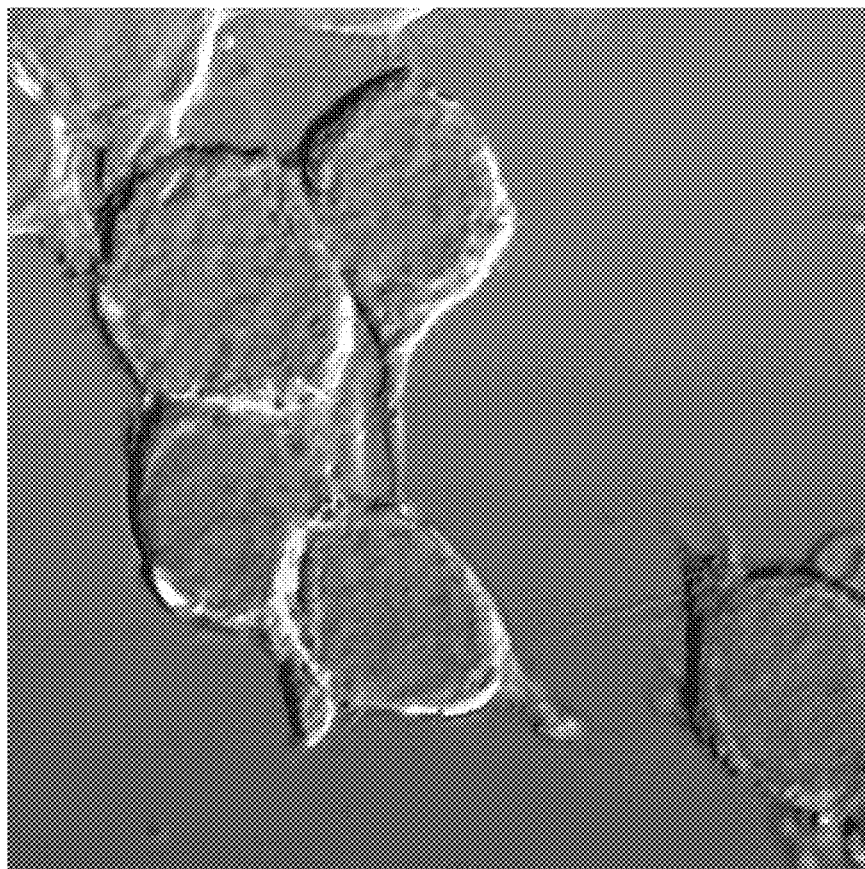


FIG. 9

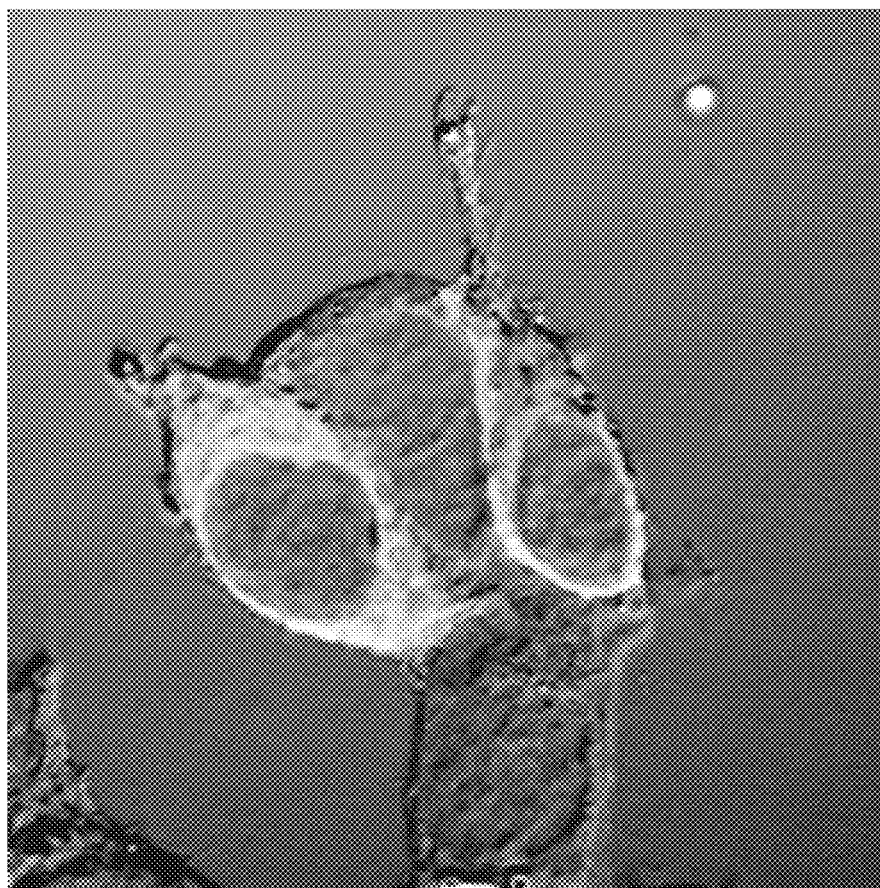


FIG. 10

LYG6F-mouse-ECD_FC_mouse IgG2a

SIQTIYVASGESVEMPCSPSPSLLGGQLLTWFRSPVAGSSTILVAQVQVDK
PVSDLRKPEPDSRYKLEFGNYSLWLEGSRDEDAGRYWCTVMDQNHKYQNRVYDVSVLKGSQFSVKSPDGP
SCAALLCSVVPARRLDSVTWLEGRNTVRGHAQYFWGEGAALLVCPTEGLPETRARRPRNIRCLLPQNKR
FSFSLAAASAEPSP TVCATLPSWDVPEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMI^{SL}SPIV
TCVVVDVSEDDPDVQISW^{FV}NNVEVHTAQ^{TQ}THREDYNSTLRVVSALPIQH^{QD}WMSGKEFKCKVNNKDLPA
PIERTISKPKGSVRAPQVYVLPPEEEMTKKQVTLTCMVTD^{FMP}EDIYVEWTNNGKTELNYKNTEPVLDSD
GSYFMYSKLRVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK

FIG. 10A

VSIG10-Mouse-ECD_FC_mouse IgG2a

LQLLLNPSRANLSVRPNSEVLPGIHPDLEAVAIGEVDNVTLRCCSASG
SRGLVTWYRNDSEPAFLVSFNSSLPPAAPRFSLEDAGALRIEALRLEDDGNYTCQEVLNETHWFPVRLRV
ASGPAYVEVNI SATGTLPNGTLYAARGSQVDFNCCSAAQPPPEVEWWIQTHSIPEFLGKNLSANSFTLML
MSQNLQGNYTCSATNVLSGRQRKVTTELLVYWPPPSAPQCSVEVSSESTTLELACNWDGGYPDPTFLWTE
EPPGTTIMGNSKLQTLSPAQLLEGKKFKCVGNHILGPESGASCVVKLSSPLLPSQPMRTCFVGCNVTLTCE
VSGANPPARIQWLRNLTQPAIQPSSHYYITQQGQSSSLTIHNCSQDLDEGFYYCQAENLVGVRATNIWLS
VKEPLNIGGEPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMI^{SL}SPIVTCVVVDVSEDDPDVQIS
W^{FV}VNNVEVHTAQ^{TQ}THREDYNSTLRVVSALPIQH^{QD}WMSGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQ
VYVLPPEEEMTKKQVTLTCMVTD^{FMP}EDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNW
ERN^SSYSCSVVHEGLHNHHTTKSFSRTPGK

FIG. 10B

TMEM25-mouse-ECD_FC_mouse IgG2a

ELAPQIDGQTWAERALRENEHHAFTCRVAGGSATPRLAWYLDGQLQEATTSRLLSVGGDAFSGGTSTFTVT
AQRSQHELNCSLQDPGSGRPNASVILNVQFKPEIAQVGAKYQEAQGPGLLVVLFALVRANPPANVTWIDQ
DGPVTVNASDFLVLDAQNYPWLTNHTVQLQLRSLAHNLSVVATNDVGVTASLPAPGLLATRIE**EPRGPTI**
KPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFNVEVHTAQTQTH
REDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPPPEEEMTKKQV
TLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNWVERNSYSCSVVHEGLN
HHTTKSFSRTPGK

FIG. 10C

LSR-mouse-ECD_FC_mouse IgG2a

IQVTVPDPYHVILFQPVTLHCTYQMSNTLTAPI
VIWKYKSFCDRVDADFSPASVDNQLNAQLAAGNPGYNPYVECDSVRTVRVVATKQGNAVTLGDYYQGR
RITITGNADLTFEQTAWGDSGVYYCSVVSAQDLDGNNEAYAELIVLGRTSEAPELLPGFRAGPLE**DEPRGP**
TIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFNVEVHTAQTQ
THREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPPPEEEMTKK
QVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNWVERNSYSCSVVHEGL
HNHHTTKSFSRTPGK

FIG. 10D

LYG6F_Human ECD_Human IgG1-Fc (C220S)

MAVLELLLFLCGTPQAADNMQAIYVALGEAVELPCSPPTLHGDEHLSWFCSPAAGSFTTLVAQVQVGRP
APDPGKPGRESRLRLLGNYSLWLEGSKEEDAGRYWCAVLGQHNYQNWRVYDVLVLKGSQLSARAADGSP
CNVLLCSVVPSRMDSVTWQEGKGPVRGRVQSFWGSEAALLVCPGEGLSEPRSRPPIIRCLMTHNKGV
SFSLAASIDASPALCAPSTGWDMPKSSDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
FLYSKLTVDKSRWQQGNVVFSCSVMEALHNHYTQKSLSLSPGK

FIG. 11A**VSIG10_Human ECD_Human IgG1-Fc (C220S)**

MAAGGSAPEPRVLVCLGALLAGWVAVGLEAVVIGEVHENVTLHCGNISGLRGQVTWYRNNSEPVFLLSSN
SSLRPAEPRFSLVDATSLHIESLSLGDEGIYTCQEILNVTQWFQVWLQVASGPYQIEVHIVATGTLPNGT
LYAARGSQVDFSCNSSSRPPPVEWWFQALNSSSESFGHNLTVNFFSLLLISPQLQGNITCLALNQLSKR
HRKVTTELLVYPPPSAPQCWAQMASGSFMLQLTCRWGGYPDPDFLWIEEPGGVIVGKSKLGVEMLSSES
QLSDGKKFKCVTSHIVGPESGASCMVQIRGPSLLSEPMKTCFTGGNVTLTCQVSGAYPPAKILWLRNLQ
PEVIIQPSSRHLITQDQGNSTLTIHNCSQDLDEGYIICRADSPVGVREMEIWL SVKEPLNIGGEPKSSDKT
HTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVVFSCSVMEALHNHY
TQKSLSLSPGK

FIG. 11B

VSIG10 Skipping exon 3_Human ECD_Human IgG1-Fc (C220S)

MAAGGSAPEPRVLVCLGALLAGWVAVGLEAVVIGEVHENVTLHCGNISGLRGQVTWYRNNSEPVFLLSSN
SSLRPAEPRFSLVDATSLHIESLSLGDEGIYTCQEILNVTQWFQVWLQVANPPPSAPQCWAQMASGSEML
QLTCRWDGGYPDPDFLWIEEPGGVIVGKSKLGVEMLSQSLSDGKKFKCVTSHIVGPESGASCMVQIRGP
SLLSEPMKTCFTGGNVTLTCQVSGAYPPAKILWLRNLTQPEVIIQPSSRHLITQDGQNSTLTIHNCSQDL
DEGYICRADSPVGVREMEIWLSVKEPLNIGGEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMIS
RTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPP
VLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

FIG. 11C**TMEM25_Human ECD_Human IgG1-Fc (C220S)**

MALPPGPAALRHTELLLPALLSSGWGELEPQIDGQTTAERALRENERHAFTCRVAGGPGTPRLAWYLDGQL
QEASTSRLLSVGGEAFSGGTSTFTVTAHRAQHELNCSLQDPRSGRSANASVILNVQFKPEIAQVGAKYQEA
QGPGLLVVLFAVLRANPPANVTWIDQDGPVTVNTSDFLVLDQNYPWLTNHTVQLQLRSLAHNLSVVATND
VGVTASASLPAPGLLATRVEEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDGDSFFLYSK
LTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

FIG. 11D

LSR isoform-a_Human ECD_Human IgG1-Fc (C220S)

**MALLAGGLSRGLGSHPAAAGRDAVVFVWLLSTWCTAPARAIQVTVSNPYHVILFQPVTLPCTYQMTST
PTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECDSVRTVRVVATKQGNAVTLGD
YYQGRRITITGNADLTFDQTAWGDSGVYYCSVVSAQDLQGNNEAYAELIVLGRTSGVAELLPGFQAGPIE
DEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRD
ELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSV
MHEALHNHYTQKSLSLSPGK**

FIG. 11E

LSR isoform-b_Human ECD_Human IgG1-Fc (C220S)

**MALLAGGLSRGLGSHPAAAGRDAVVFVWLLSTWCTAPARAIQVTVSNPYHVILFQPVTLPCTYQMTST
PTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECDSVRTVRVVATKQGNAVTLGD
YYQGRRITITGNADLTFDQTAWGDSGVYYCSVVSAQDLQGNNEAYAELIVLDEPKSSDKTHTCPPCPAEL
LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGK**

FIG. 11F

LSR isoform-c_Human ECD_Human IgG1-Fc (C220S)

MALLAGGLSRGLGSHPAAGRD**AVFVWLLSTWCTAPARA** IQVTVSNPYHVILFQPVTL PCTYQMTST
PTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVEQCDSVRTVRV VATKQGNVTLGD
YYQGRRITITGNADLTFDQTAWGDSGVYYCSVVSAQDLQGNNEAYAE LIVLVYAAGKAATSGVPSIYAPS
TYAHLSPAKTPPPPAMIPMGPAYNGYPGGYPGDVDRSSSAGGQGSYVPLL RDTDSSVASEVRSGYRIQAS
QQDDSMRVLYYMEKELANFDPSRPGPPSGRVERAMSEVTS LHEDDWRSRPSRGPALTPIRDEEWGGHSPR
SPRGWDQEPAREQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSP TSNGGRSRAYMPPRSRSRDDLYD
QQDSRDFPRS RDPHYDDFRSRERPPADPRSHHHRTRDPRDNGSRSGDLPYDGRLL EEA VRKKGSEERRRP
HKEEEEEAYYPPAPPYSETDSQASRERRLKKNLALSRESLVV EPKSSDKTHTCPPCPAPELLGGPSVFLF
PPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
NGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNG
QPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK

FIG. 11G**LSR isoform-d_Human ECD_Human IgG1-Fc (C220S)**

MALLAGGLSRGLGSHPAAGRD**AVFVWLLSTWCTAPARA** IQVTVSNPYHVILFQPVTL PCTYQMTST
PTQPIVIWKYKSFCDRIADAFSPASVDNQLNAQLAAGNPGYNPYVEQCDSVRTVRV VATKQGNVTLGD
YYQGRRITITGNADLTFDQTAWGDSGVYYCSVVSAQDLQGNNE AYAELIVLVYAAGKAATSGVPSIYAPS
TYAHLSPAKTPPPPAMIPMGPAYNGYPGGYPGDVDRSSSAGGQGSYVPLL RDTDSSVASVRSGYRIQASQ
QQDDSMRVLYYMEKELANFDPSRPGPPSGRVERAMSEVTS LHEDDWRSRPSRGPALTPIRDEEWGGHSPRS
PRGWDQEPAREQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSP TSNGGRSRAYMPPRSRSRDDLYDQ
DDSRDFPRS RDPHYDDFRSRERPPADPRSHHHRTRDPRDNGSRSGDLPYDGRLL EEA VRKKGSEERRRPH
KEEEEEAYYPPAPPYSETDSQASRERRLKKNLALSRESLVV EPKSSDKTHTCPPCPAPELLGGPSVFLFPPKP
KDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPGK

FIG. 11H

LSR isoform-e_Human ECD_Human IgG1-Fc (C220S)

MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARAIQVTVSNPYHVILFQPVTLPCTYQMTST
PTQPIVIWKYSFCRDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECQDSVRTVRVVATKQGNAVTLGD
YYQGRRITITGMYAAGKAATSGVPSIYAPSTYAHLSPAKTPPPPAMIPMGPAYNGYPGGYPGDVDRSSSA
GGQGSYVPLLRDTDSSVASEVRSGYRIQASQQDDSMRVLYMEKELANFDPSRPGPPSGRVERAMSEVTS
LHEDDWRSRPSRGPALTPIRDEEWGGHSPRSPRGWDQEPAREQAGGGWRARRPRARSVDALDDLTPPSTA
ESGSRSPTSNGGRSRAYMPPRSRDDLYDQDDSRDFFRSRDPHYDDFRSRERPPADPRSHHTRDPRD
NGSRSGDLPYDGRLLEEAVRKKGSEERRRPHKEEEEEAYPPAPPPYSETDSQASRERRLKKNLALSRES
LWEPKSSDKTHTCPPCPAELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV
HNATKPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAIEKTISKAGQPREPQVTLPPSR
DELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQNVFSCS
VMHEALHNHYTQKSLSLSPGK

FIG. 11I**LSR isoform-f_Human ECD_Human IgG1-Fc (C220S)**

MALLAGGLSRGLGSHPAAGRDAVVFVWLLSTWCTAPARAIQVTVSNPYHVILFQPVTLPCTYQMTST
PTQPIVIWKYSFCRDRIADAFSPASVDNQLNAQLAAGNPGYNPYVECQDSVRTVRVVATKQGNAVTLGD
YYQGRRITITGNADLTFDQTAWGDSGVYYCSVVSAQDLQGNNEAYAELIVLGRTSGVAELLPGFQAGPIE
VYAAGKAATSGVPSIYAPSTYAHLSPAKTPPPPAMIPMGPAYNGYPGGYPGDVDRSSSAGGQGSYVPLLR
DTDSSVASEVRSGYRIQASQQDDSMRVLYMEKELANFDPSRPGPPSGRVERAMSEVTSLHEDDWRSRPS
RGPALTPIRDEEWGGHSPRSPRGWDQEPAREQAGGGWRARRPRARSVDALDDLTPPSTAESGSRSPTSNG
GRSRAYMPPRSRDDLYDQDDSRDFFRSRDPHYDDFRSRERPPADPRSHHTRDPRDNGSRSGDLPYD
GRLLEEAVRKKGSEERRRPHKEEEEEAYPPAPPPYSETDSQASRERRLKKNLALSRESLVEPKSSDKTH
TCPPCPAELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ
YNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAIEKTISKAGQPREPQVTLPPSR
DELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQNVFSCS
VMHEALHNHYTQKSLSLSPGK

FIG. 11J

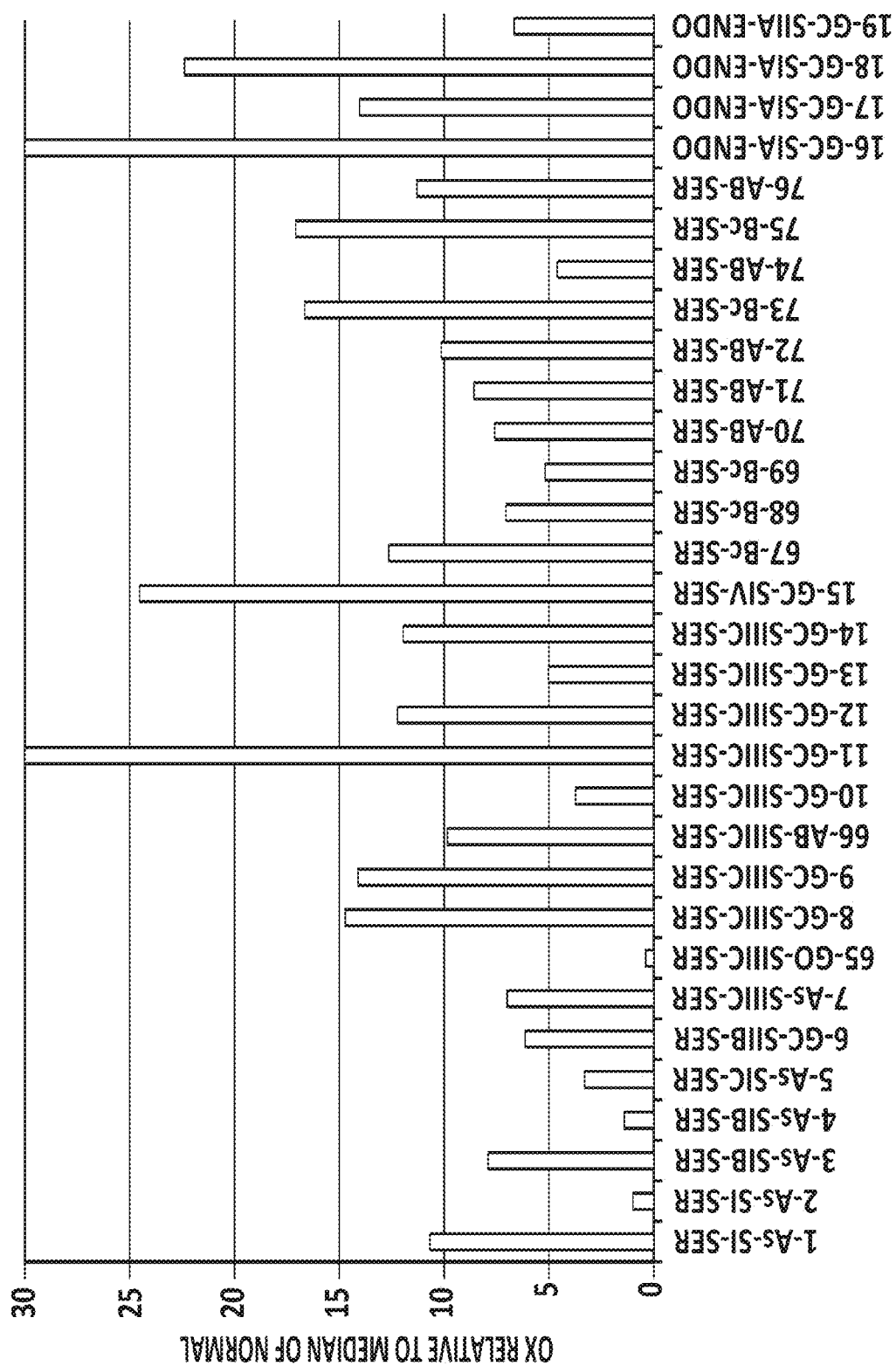
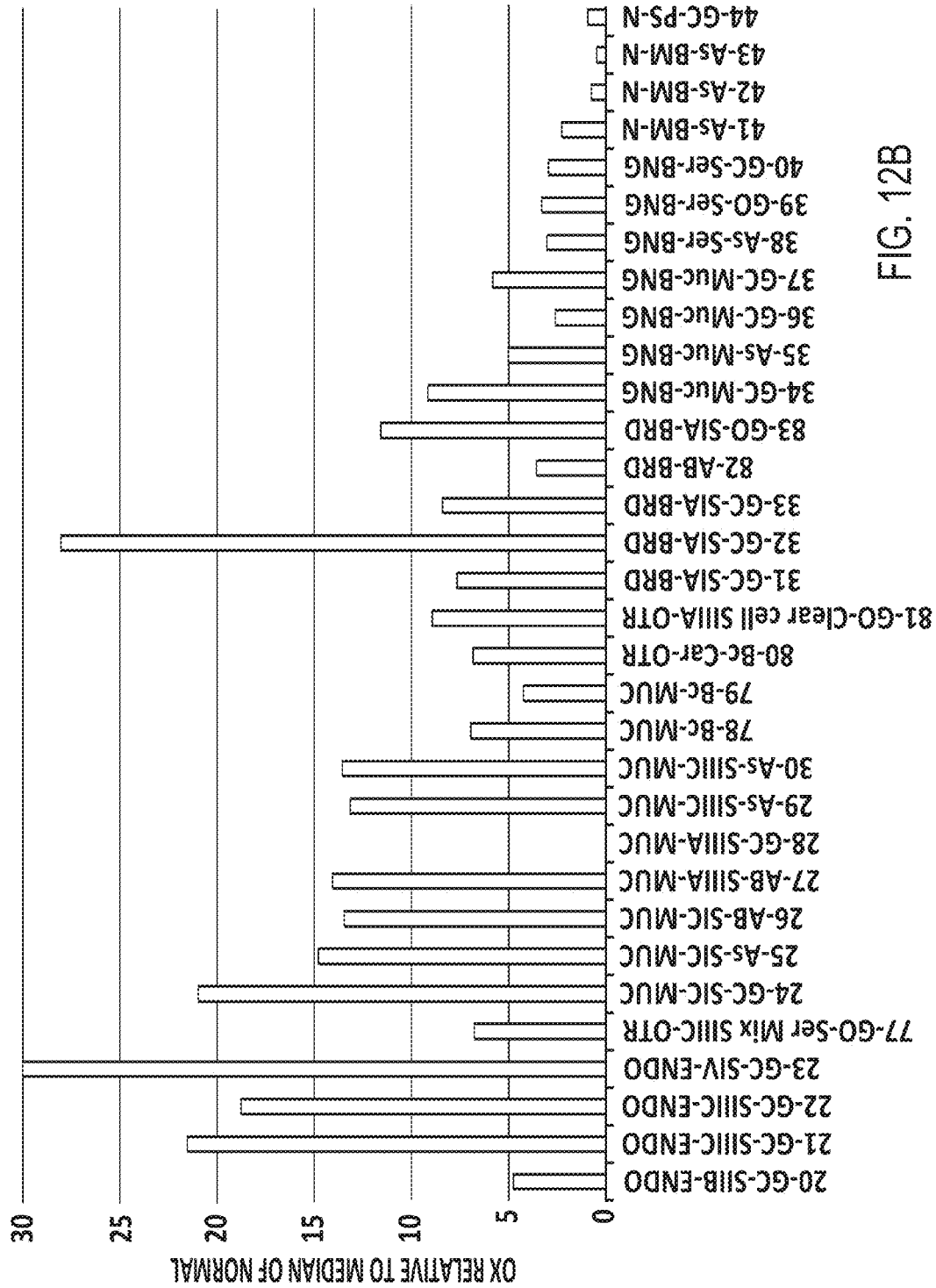


FIG. 12A



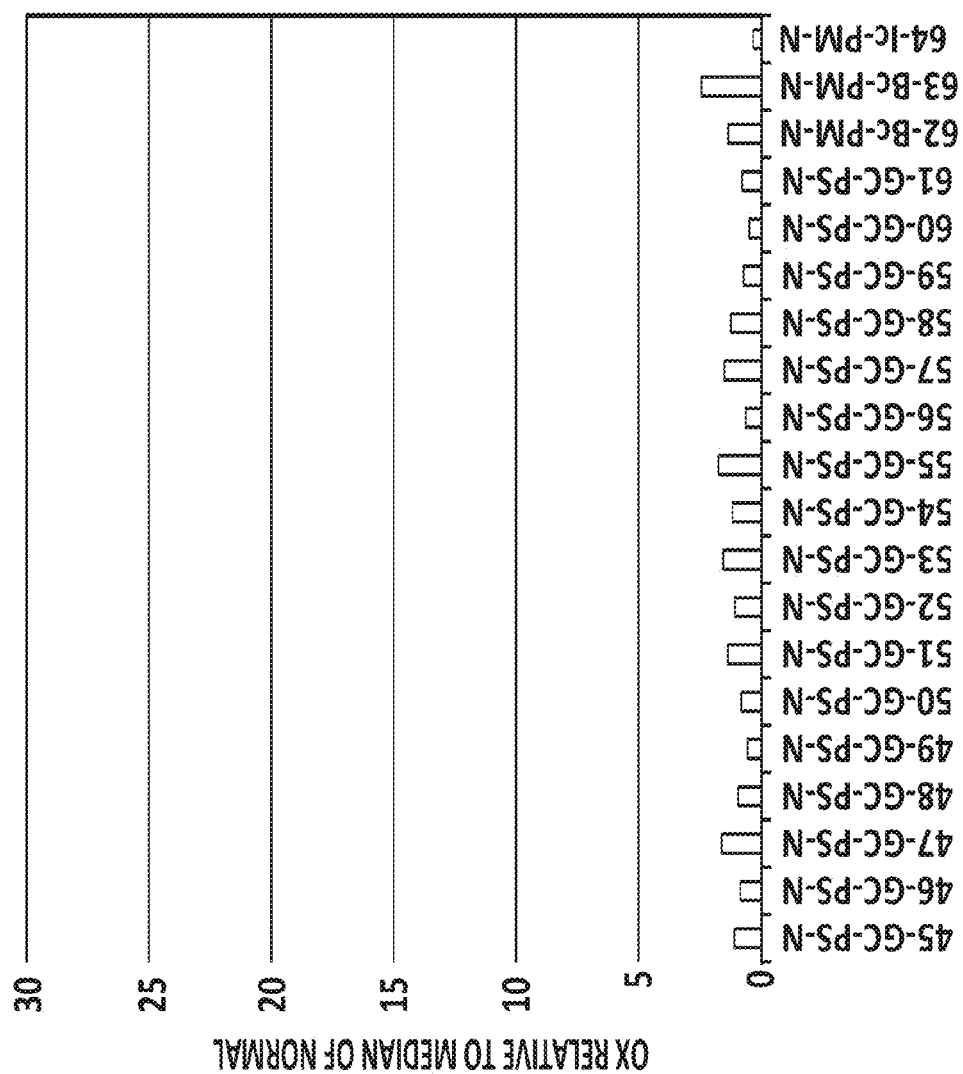
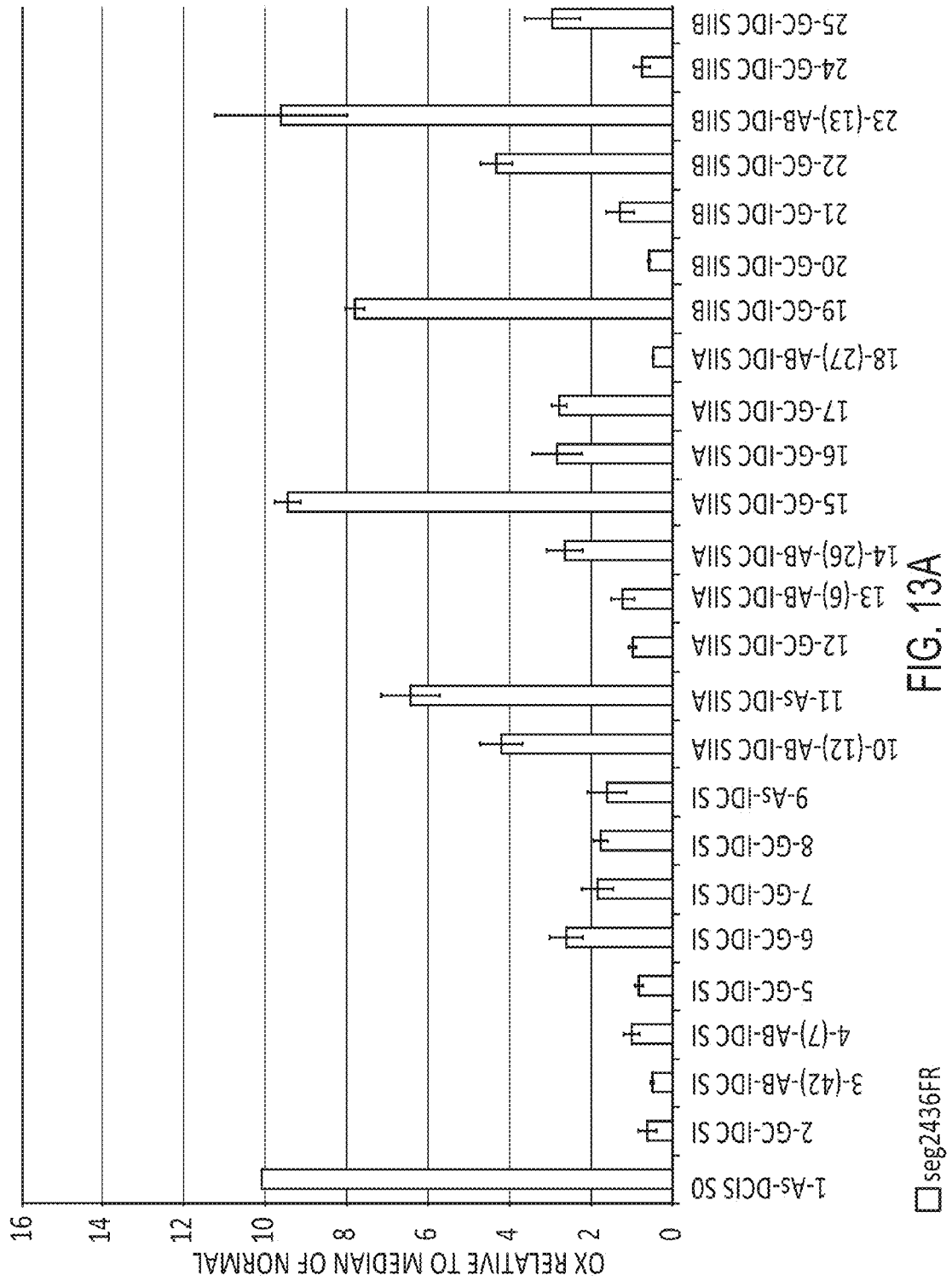


FIG. 12C



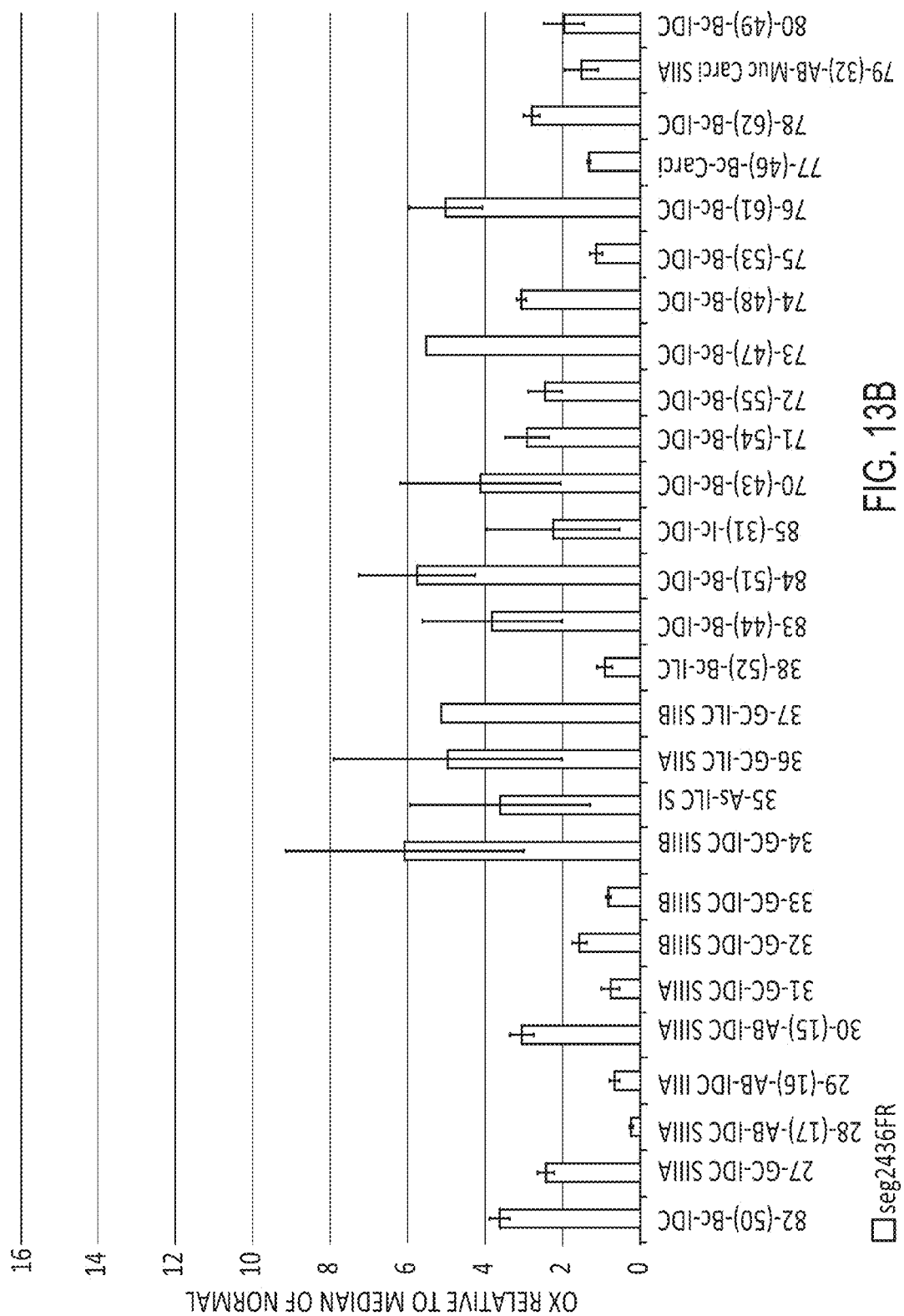
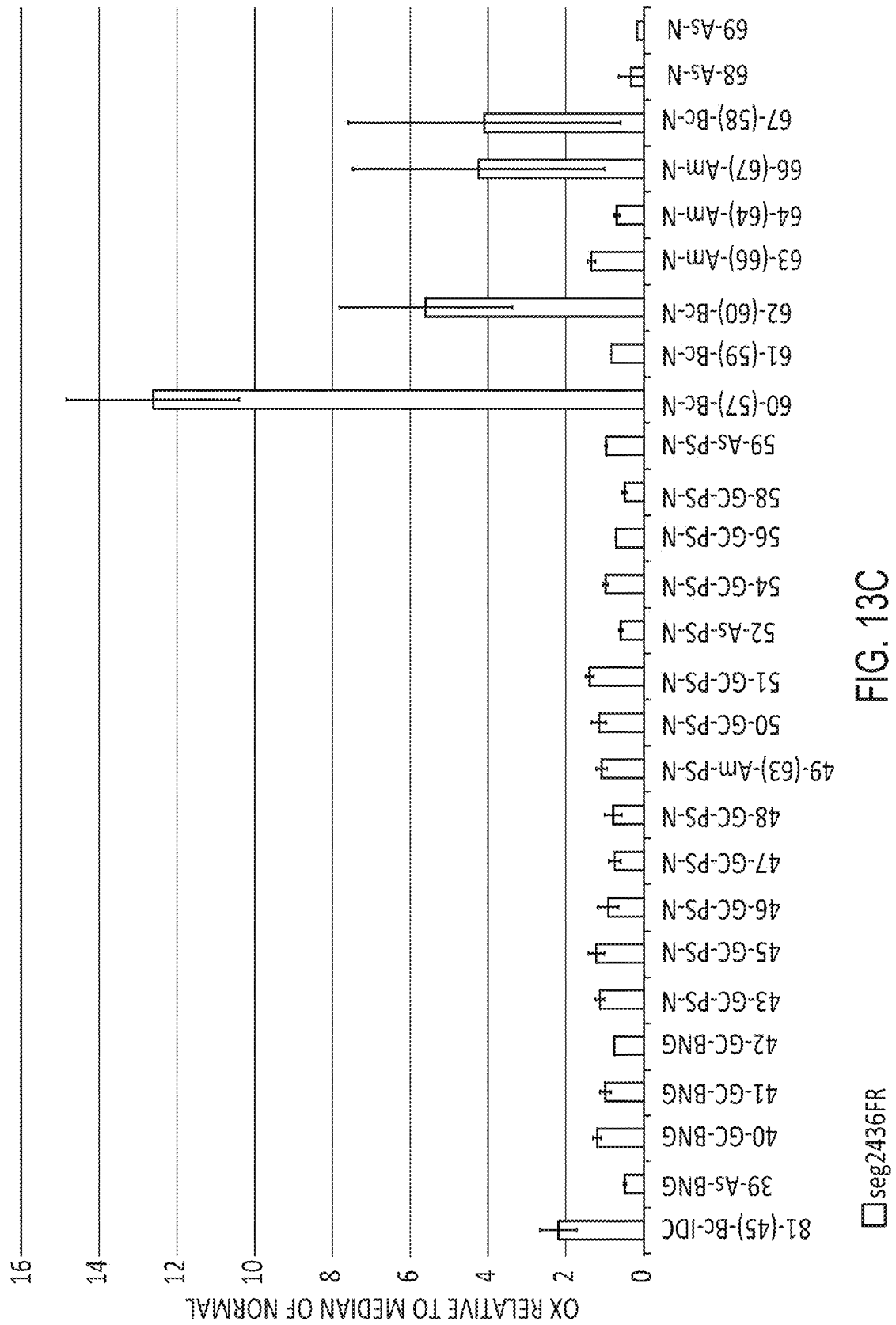


FIG. 13B



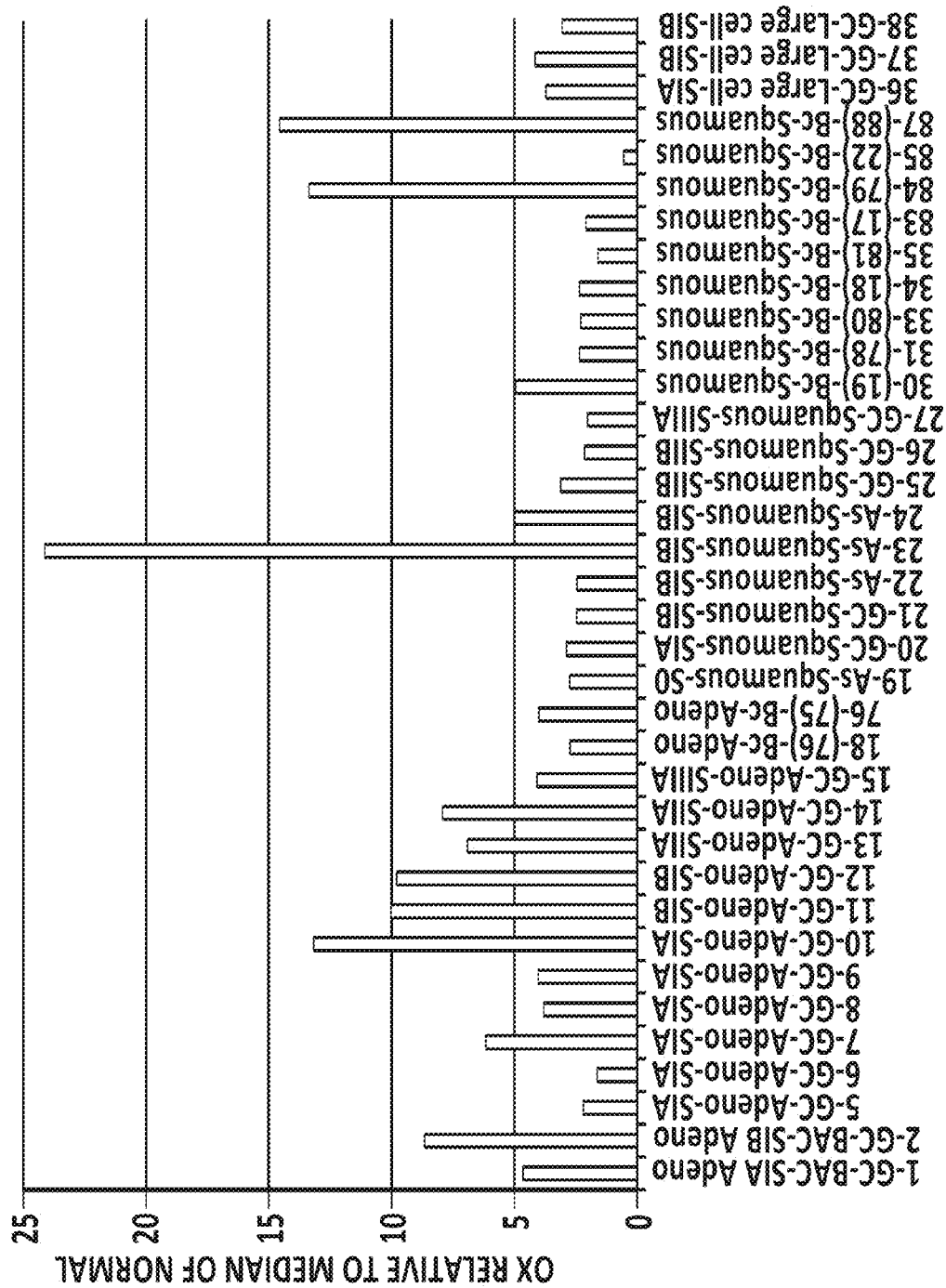


FIG. 14A

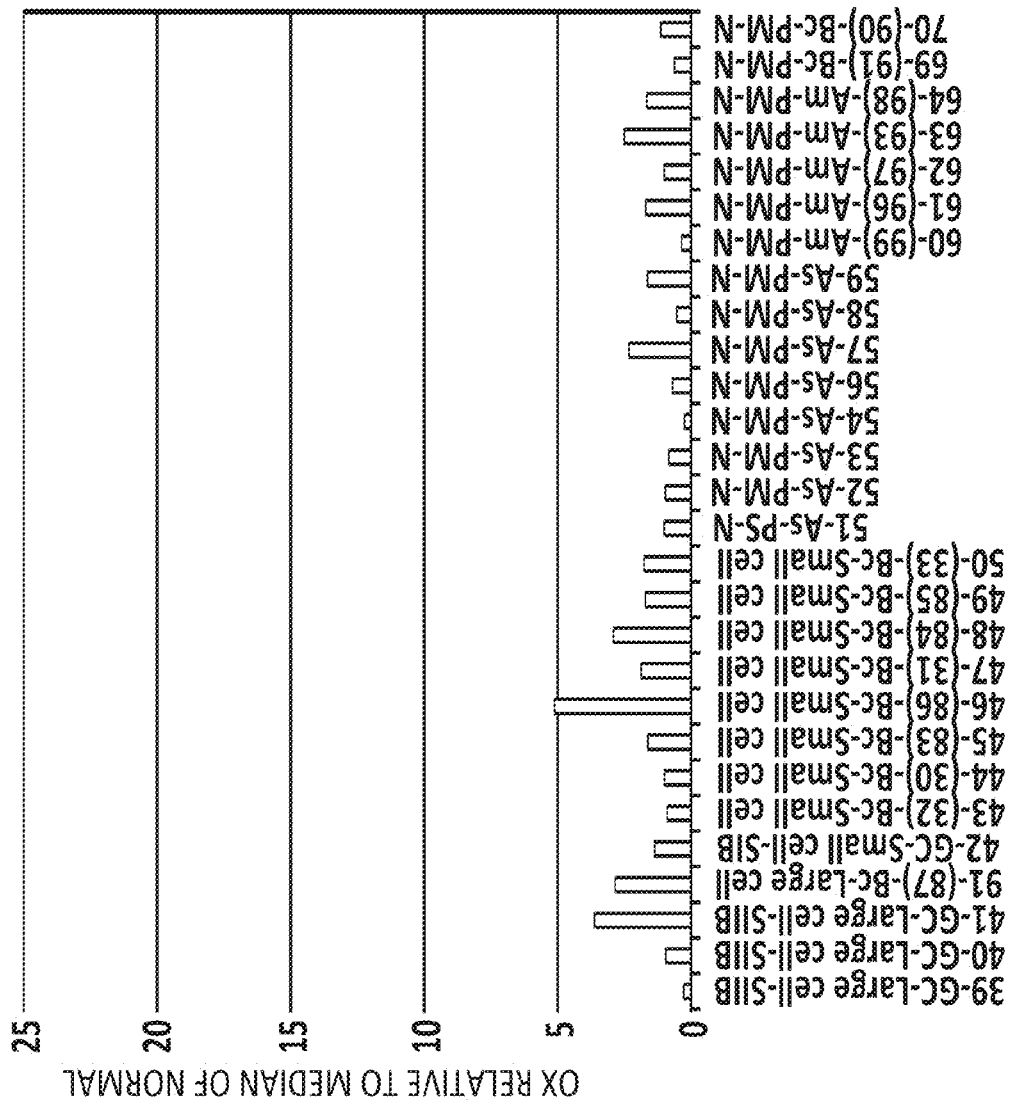


FIG. 14B

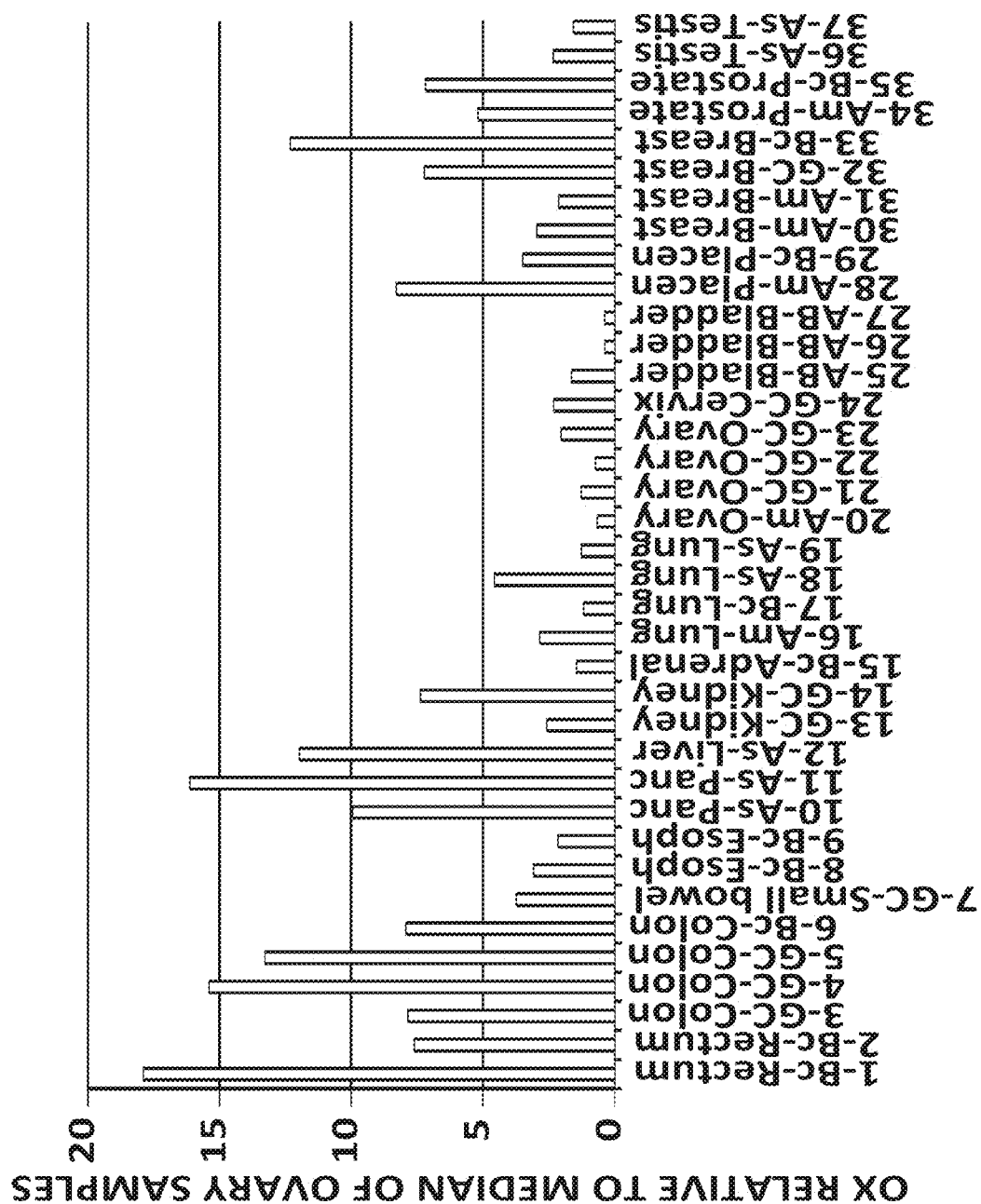
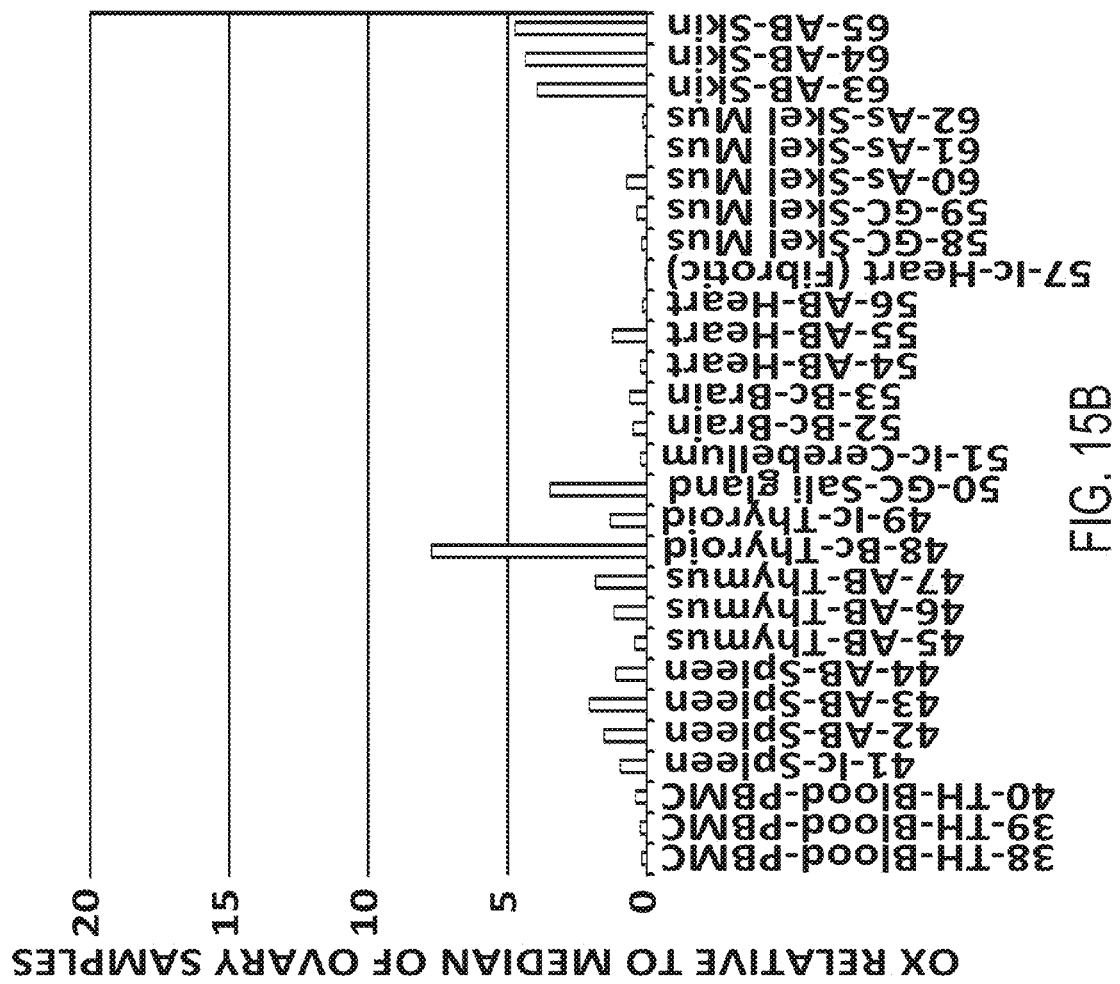
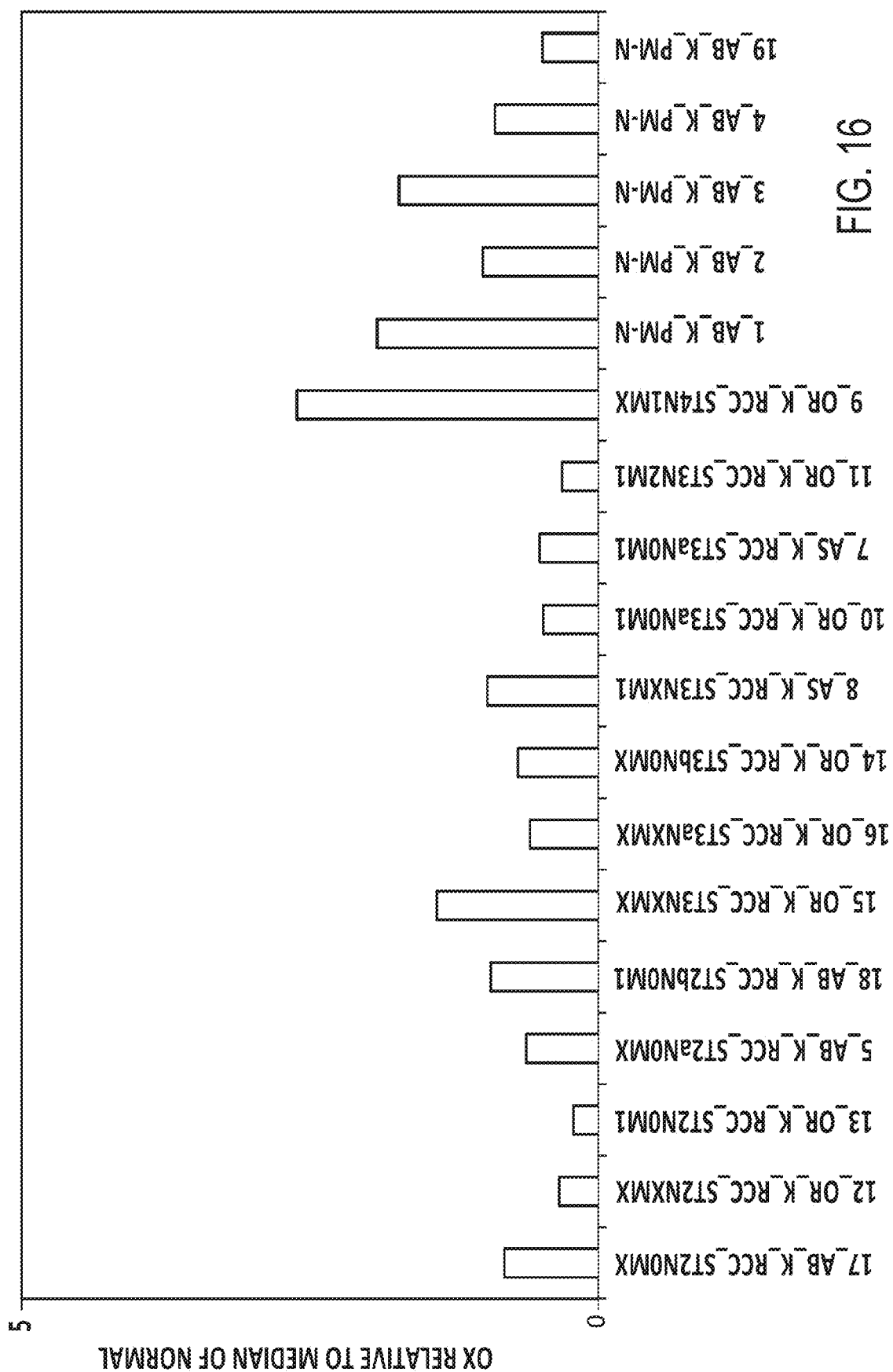
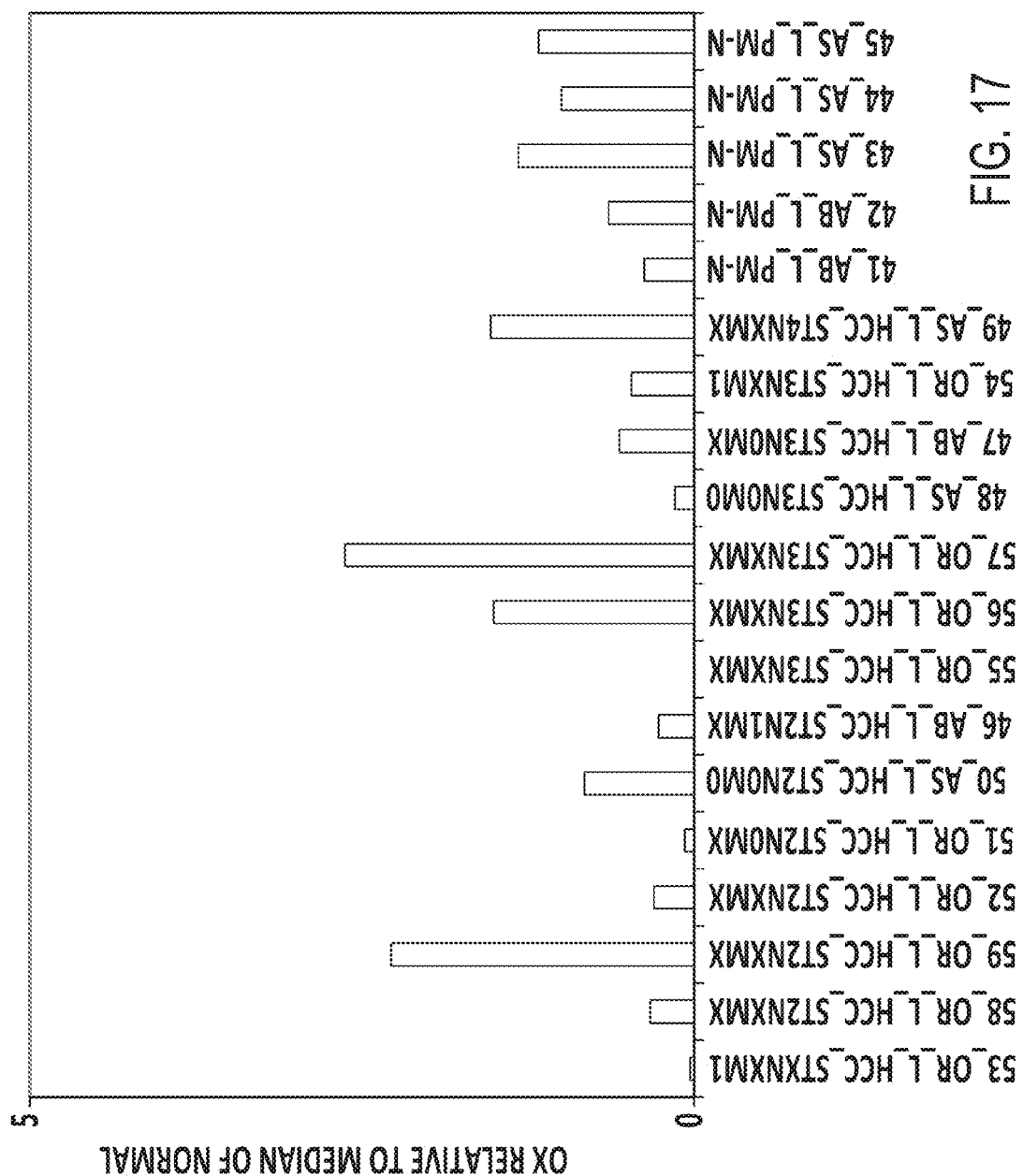


FIG. 15A







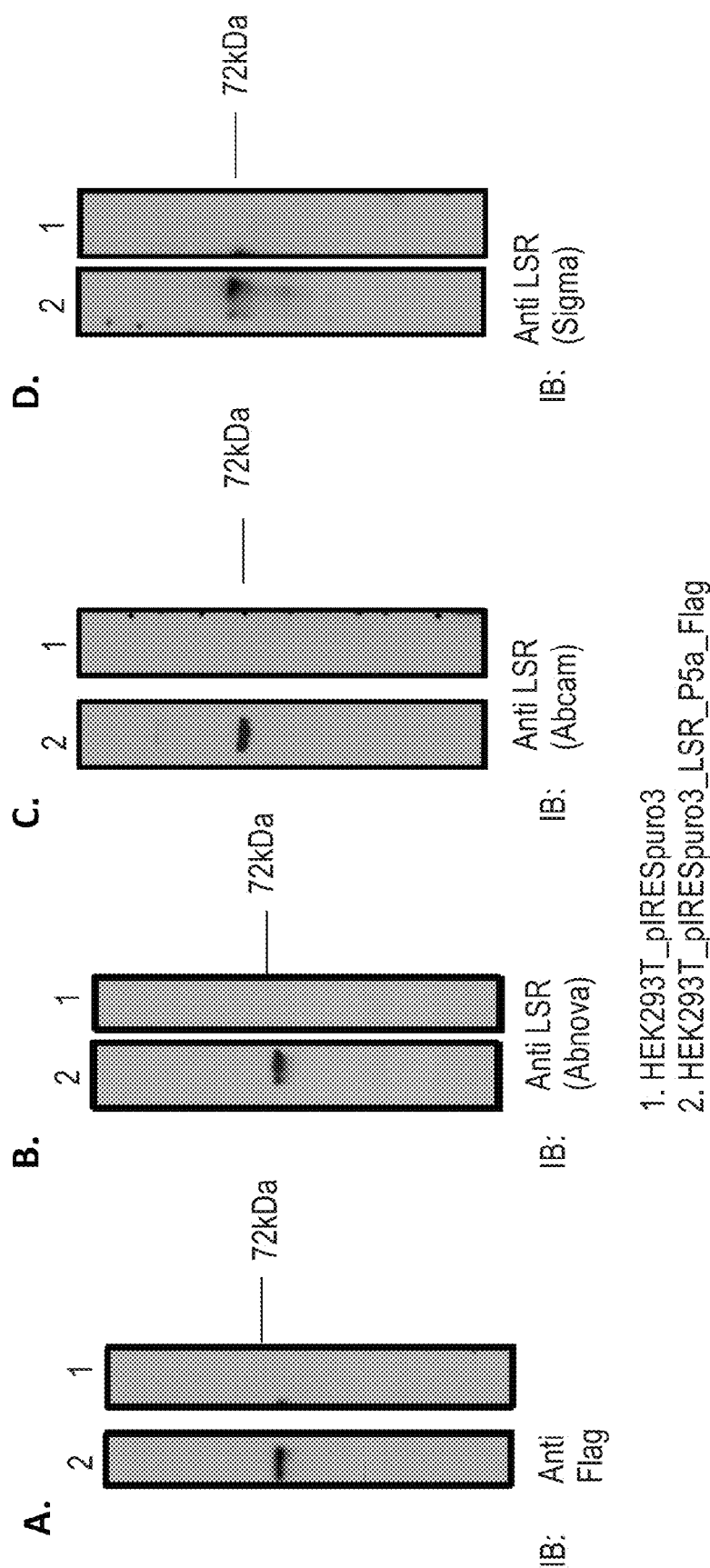


FIG. 18

FIG. 19A

Anti Flag

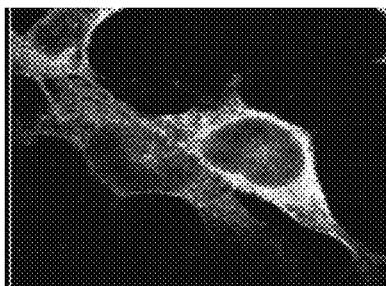


FIG. 19B

Anti LSR (Abcam)

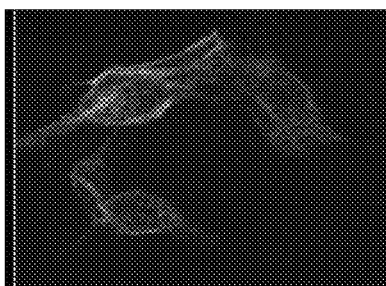


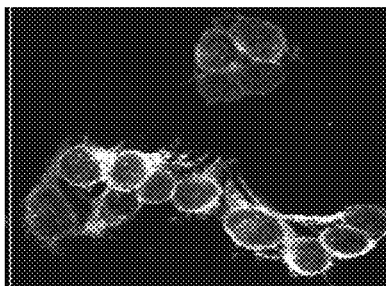
FIG. 19C

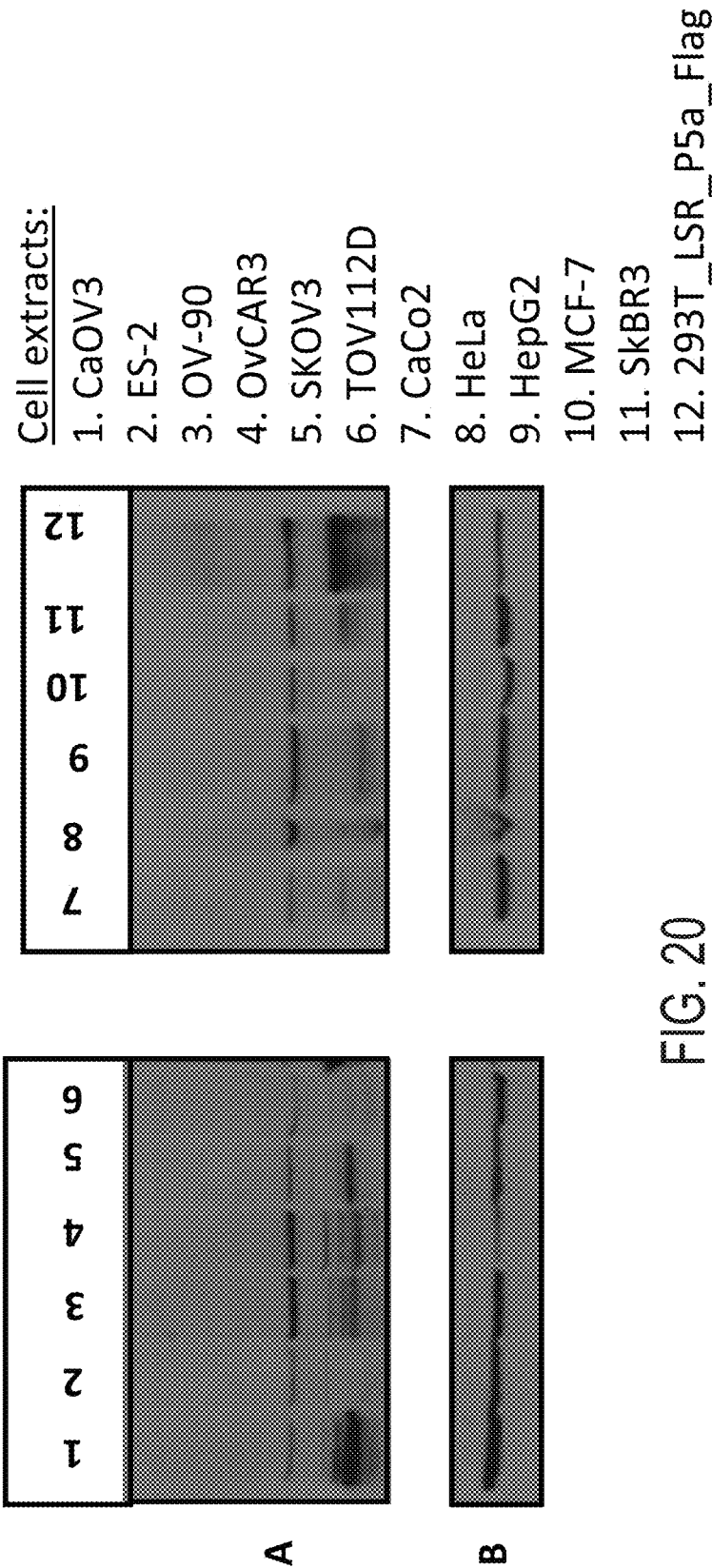
Anti LSR (Abnova)



FIG. 19D

Anti LSR (Sigma)





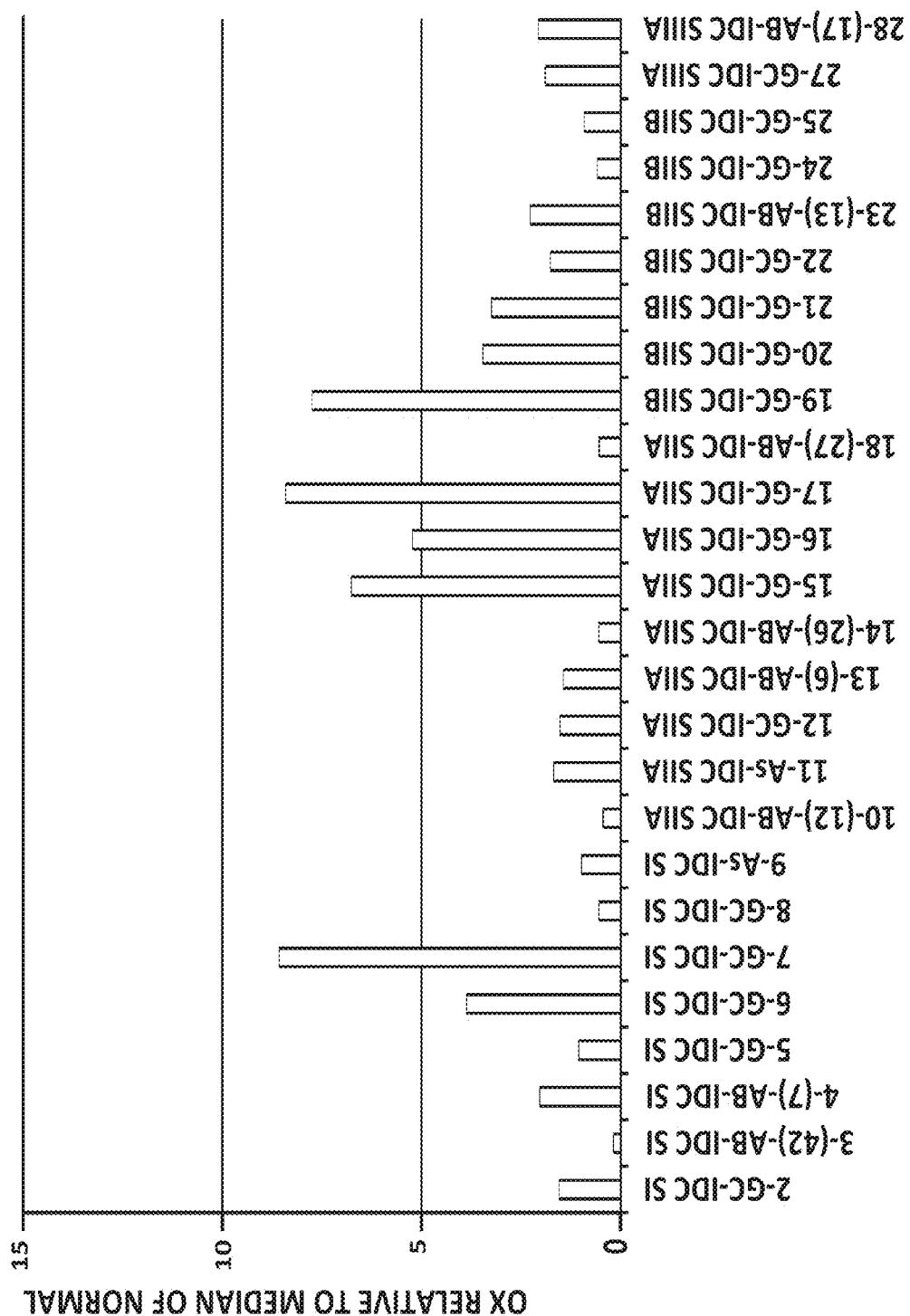
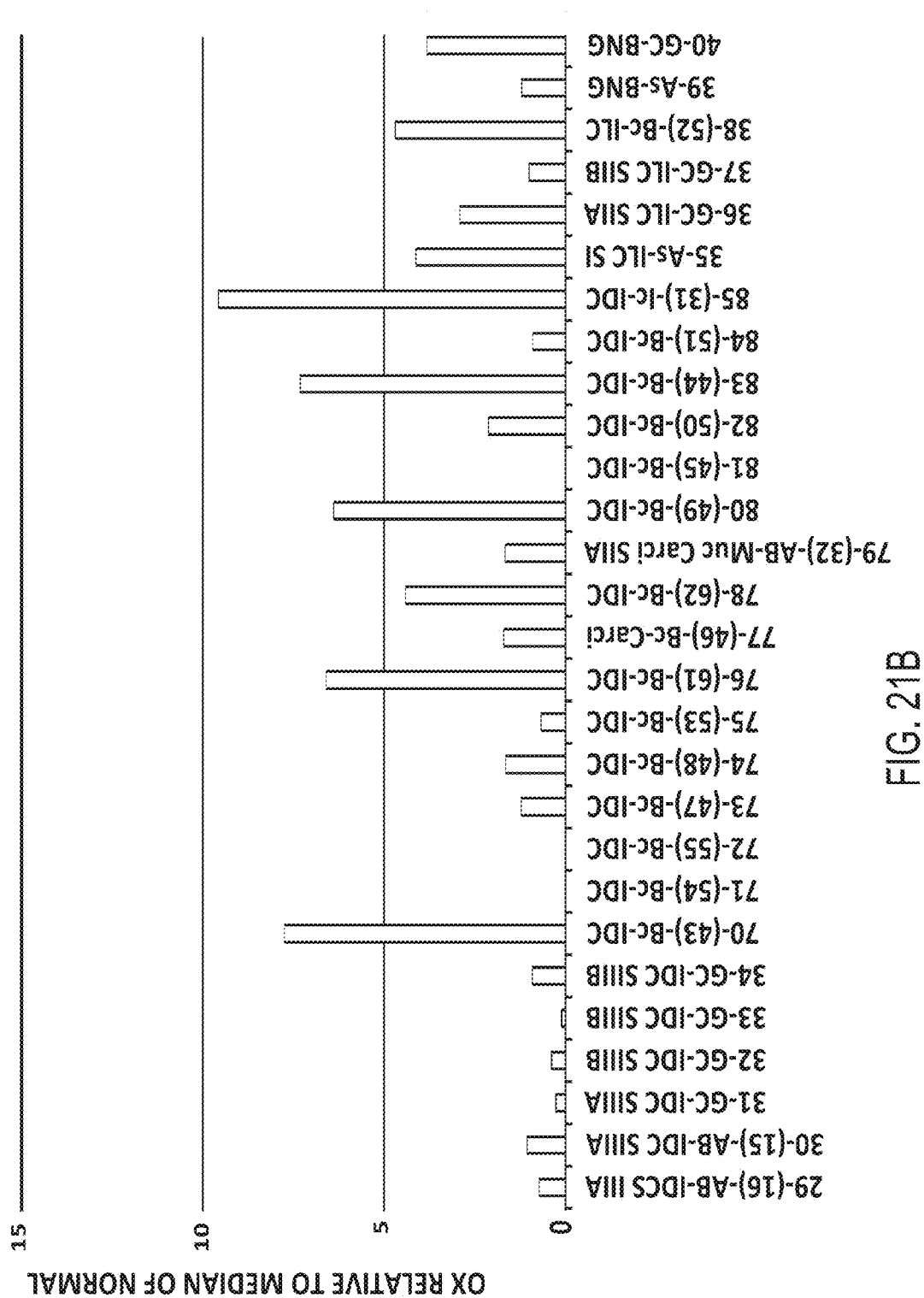


FIG. 21A



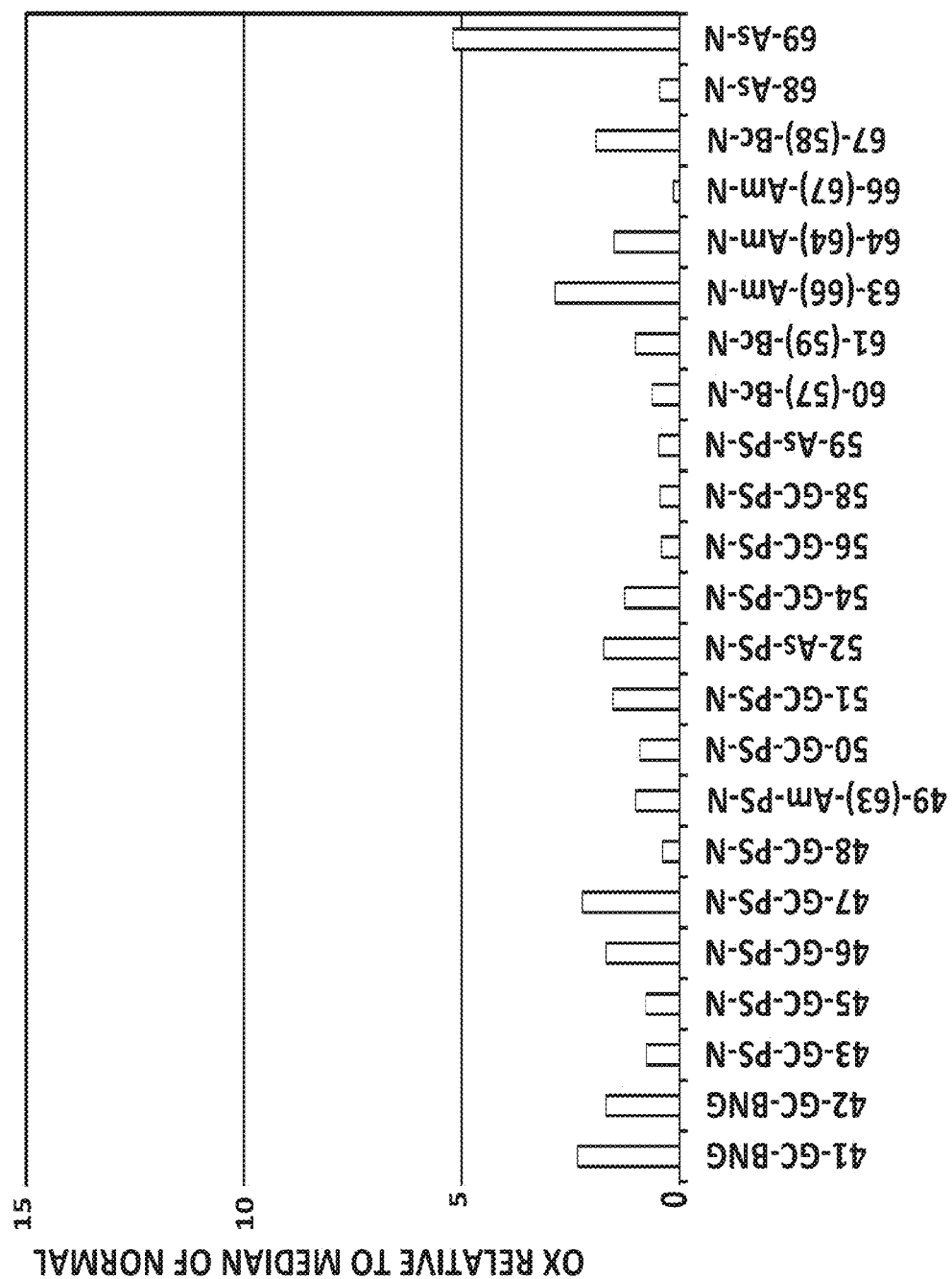


FIG. 21C

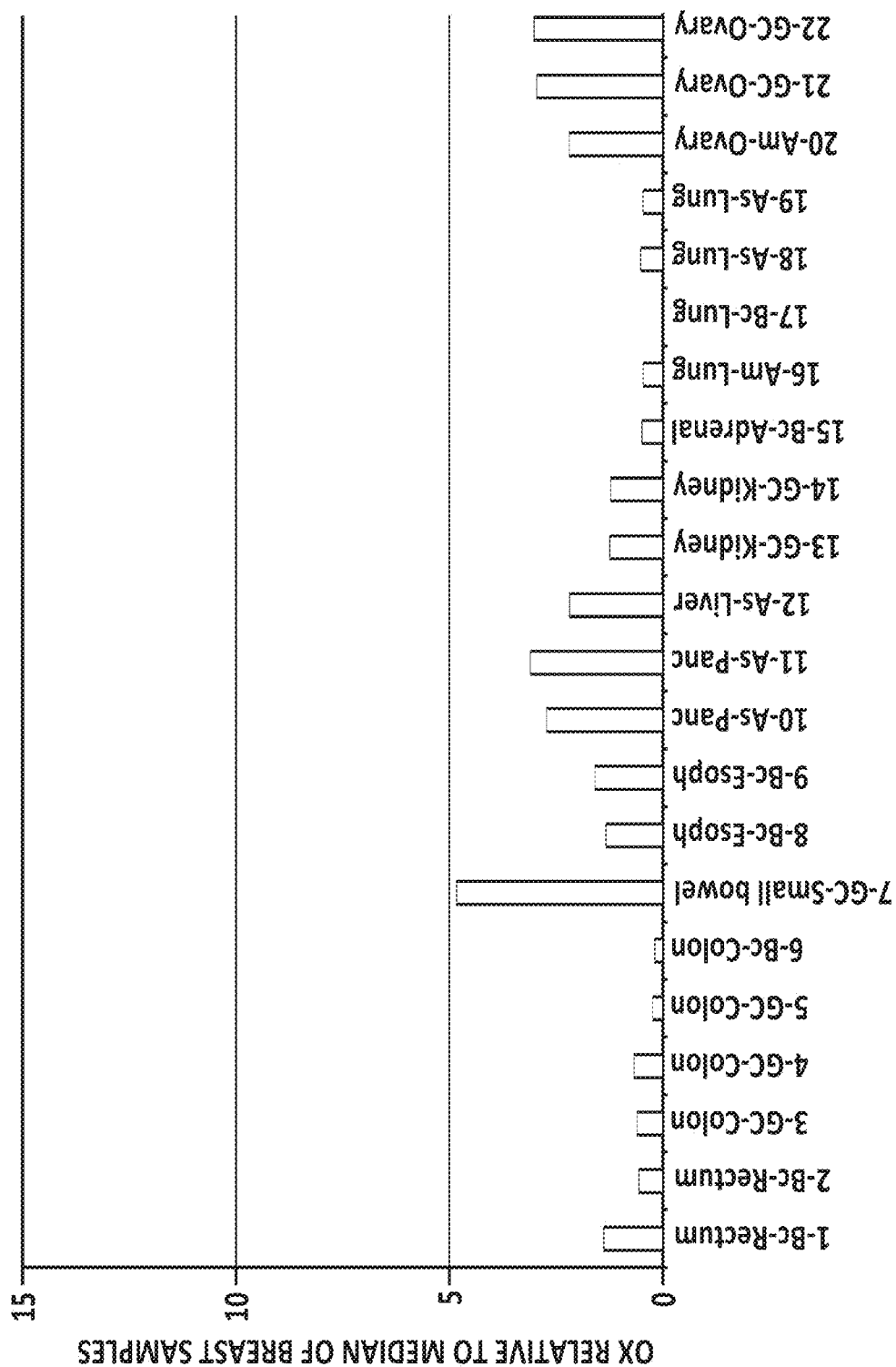


FIG. 22A

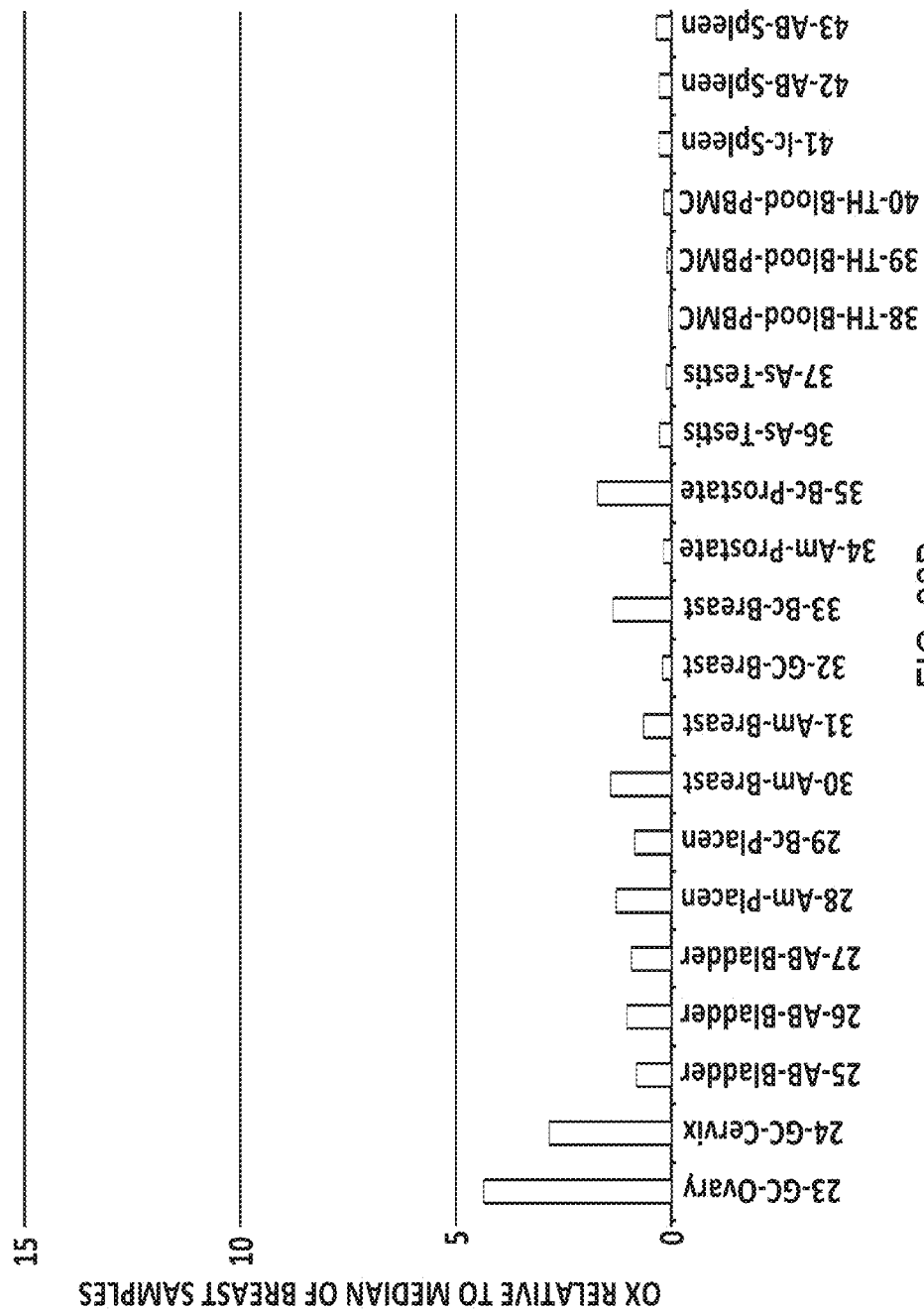
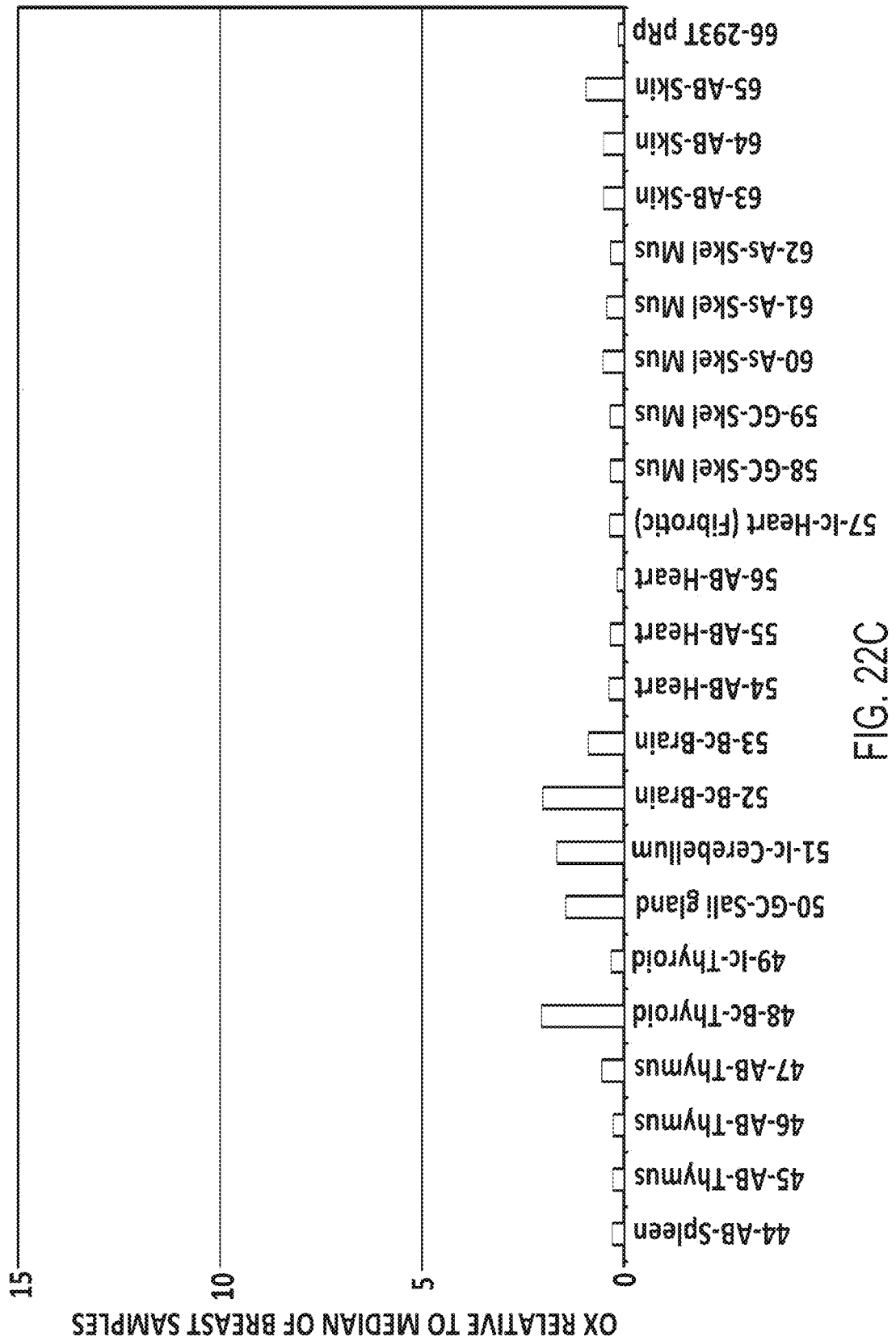


FIG. 22B



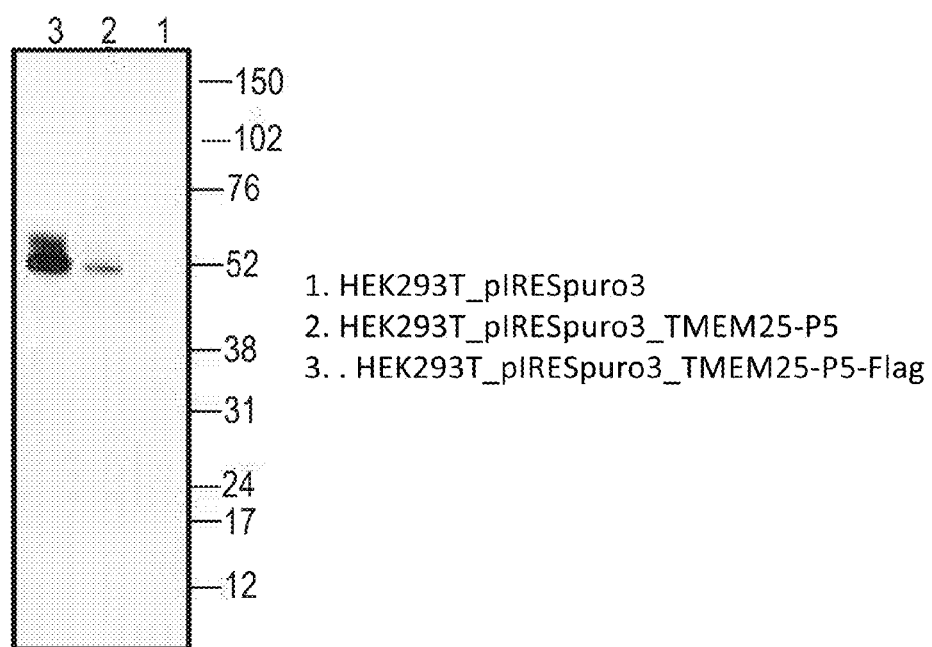


FIG. 23A

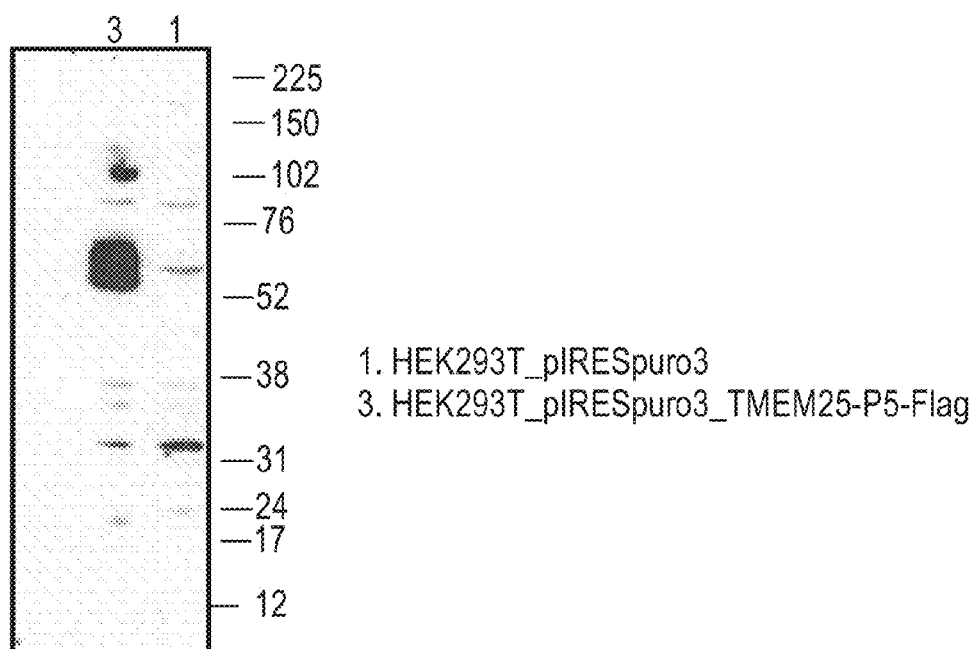


FIG. 23B

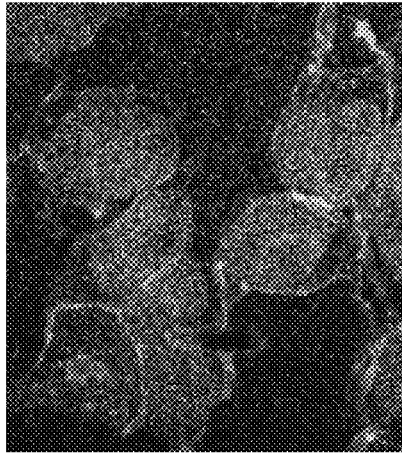


FIG. 24C

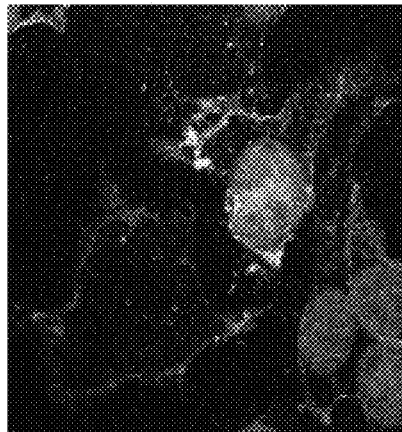


FIG. 24B

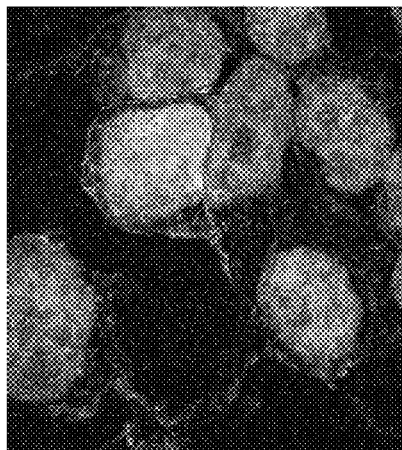


FIG. 24A

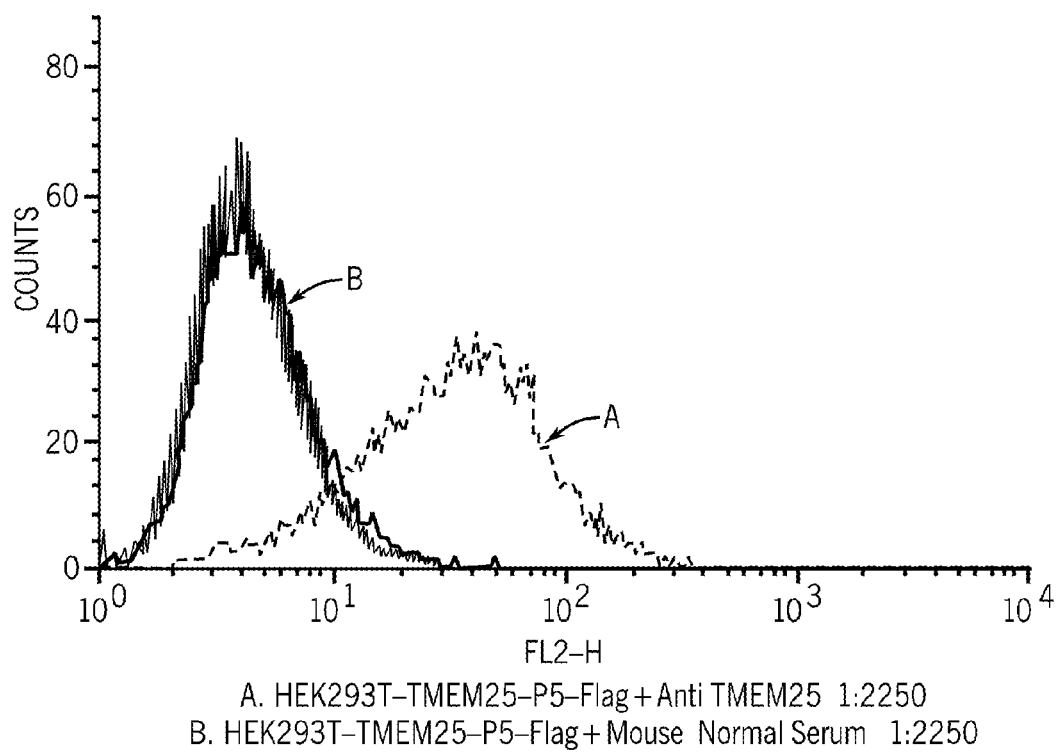
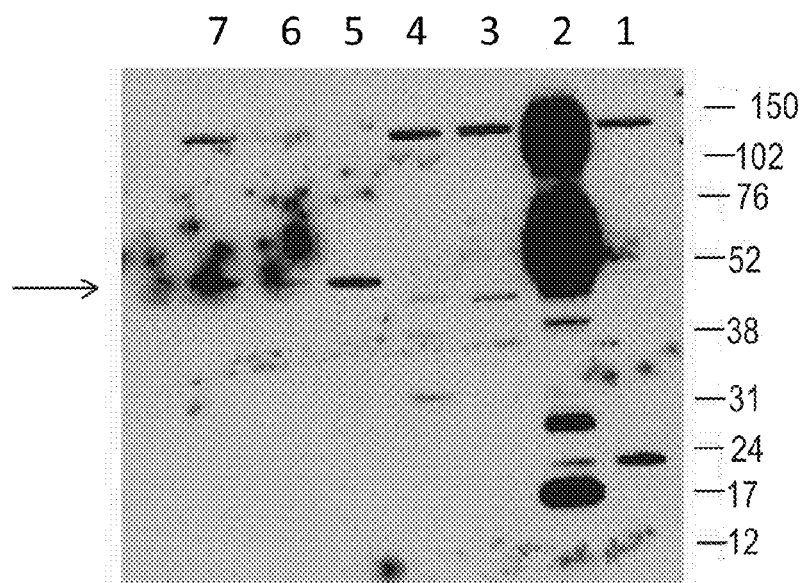
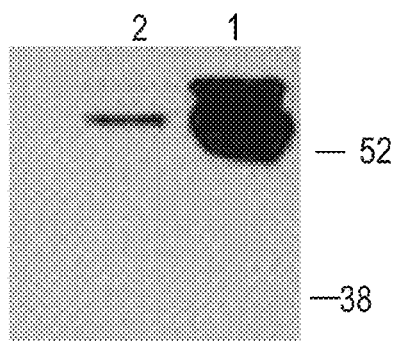


FIG. 25



1. HEK293T_pIRESpuro3
2. HEK293T_pIRESpuro3_TMEM25-P5-Flag
3. KARPAS
4. G-361
5. RPMI8226
6. DAUDI
7. JURKAT

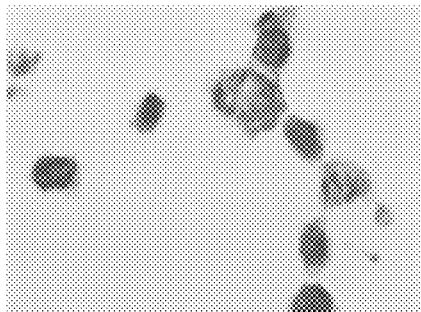
FIG. 26



1. HEK293T_pIRESpuro3_TMEM25-P5-Flag + Si scrambled
2. HEK293T_pIRESpuro3_TMEM25-P5-Flag + Si TMEM25

FIG. 27

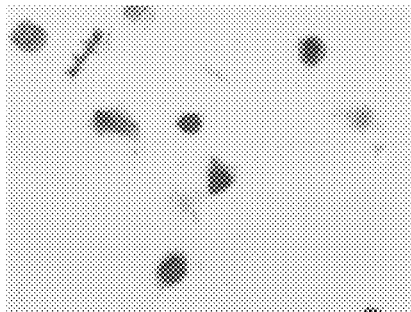
1



3 μ g/ml ANTIBODY

FIG. 28A

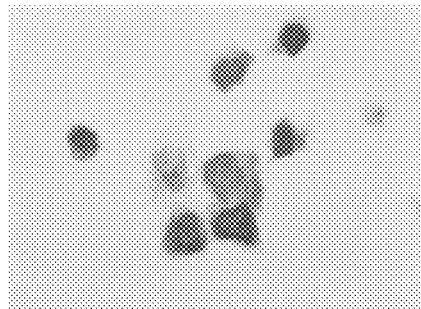
2



3 μ g/ml ANTIBODY

FIG. 28B

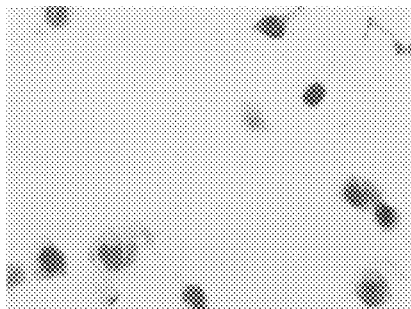
1



1 μ g/ml ANTIBODY

FIG. 28C

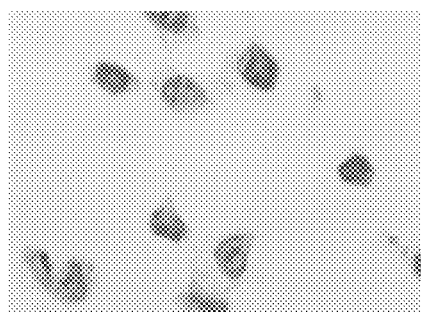
2



1 μ g/ml ANTIBODY

FIG. 28D

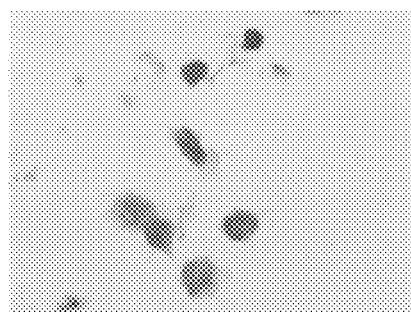
1



0.3 μ g/ml ANTIBODY

FIG. 28E

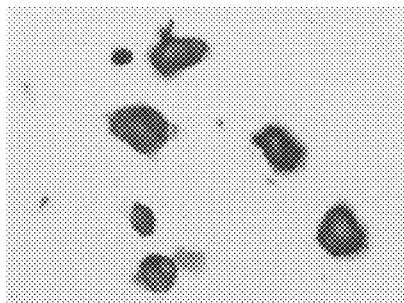
2



0.3 μ g/ml ANTIBODY

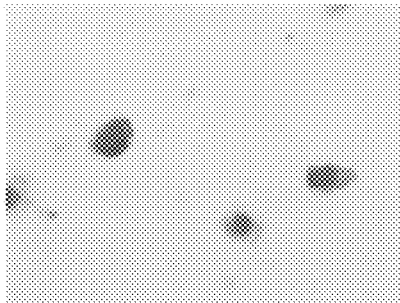
FIG. 28F

1



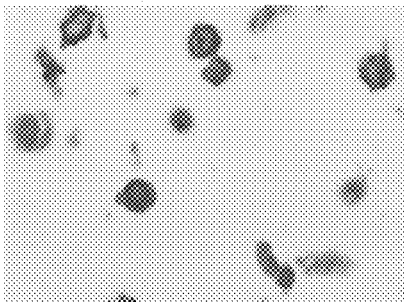
3 μ g/ml ANTIBODY
FIG. 29A

2



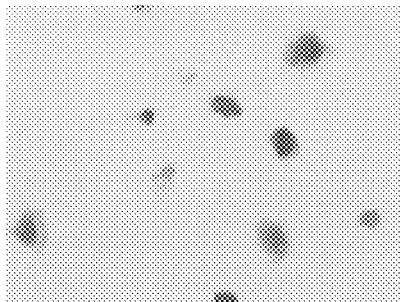
3 μ g/ml ANTIBODY
FIG. 29B

1



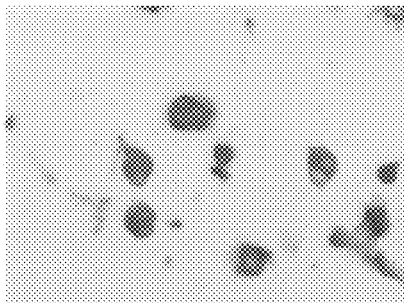
1 μ g/ml ANTIBODY
FIG. 29C

2



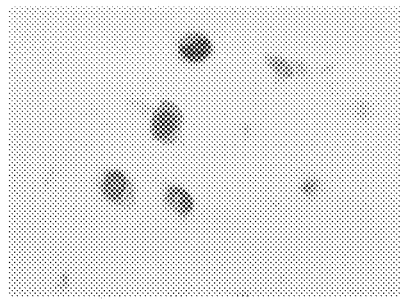
1 μ g/ml ANTIBODY
FIG. 29D

1



0.3 μ g/ml ANTIBODY
FIG. 29E

2



0.3 μ g/ml ANTIBODY
FIG. 29F

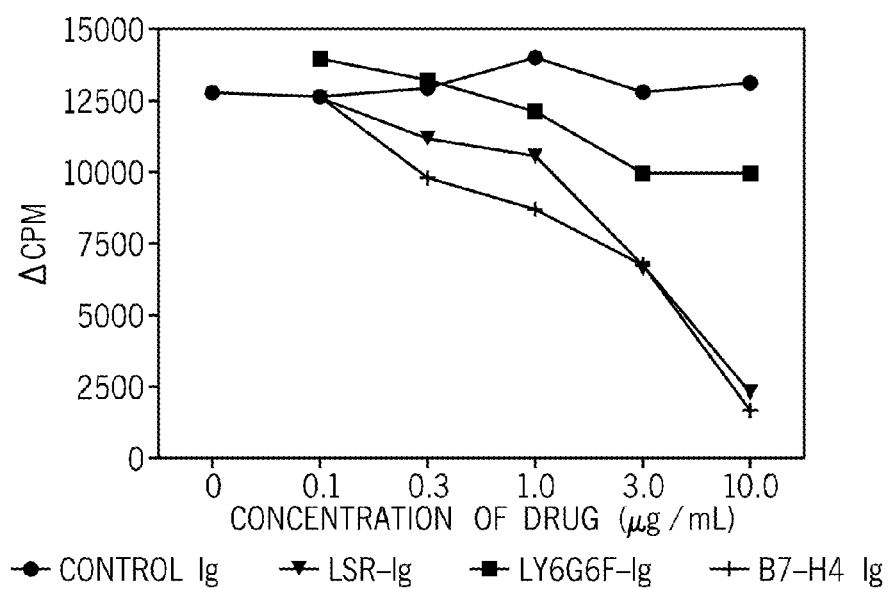


FIG. 30A

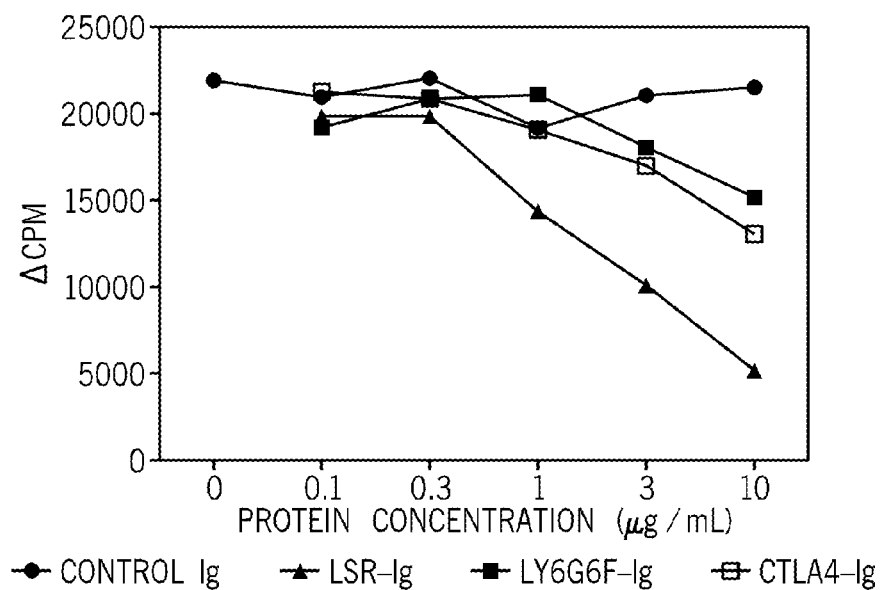


FIG. 30B

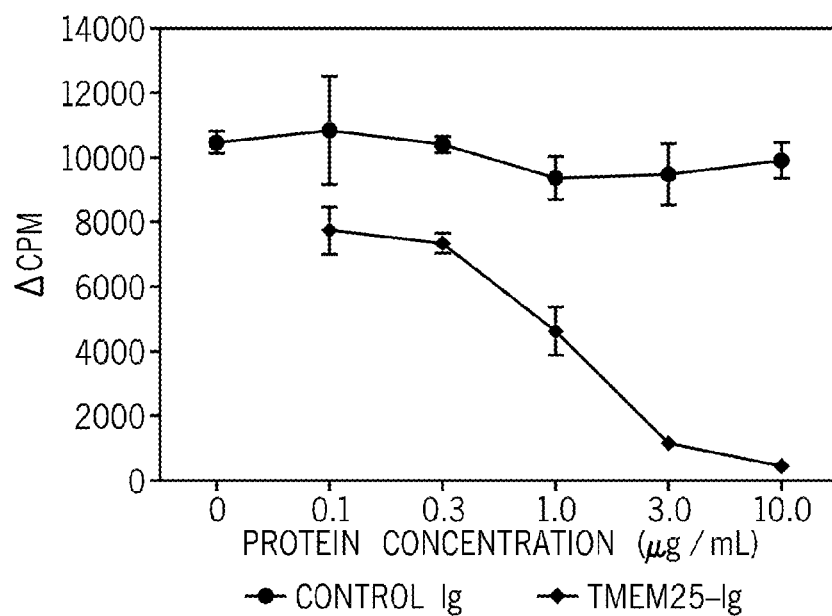


FIG. 30C

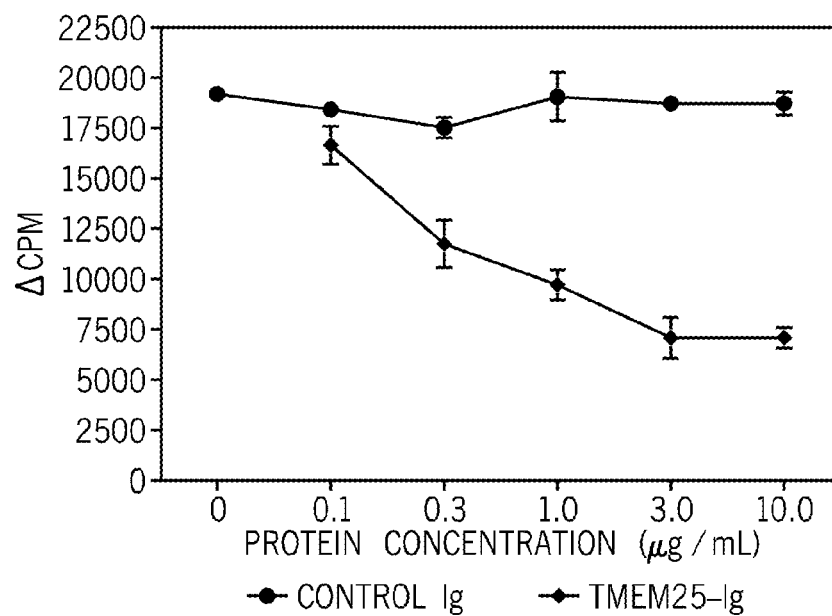


FIG. 30D

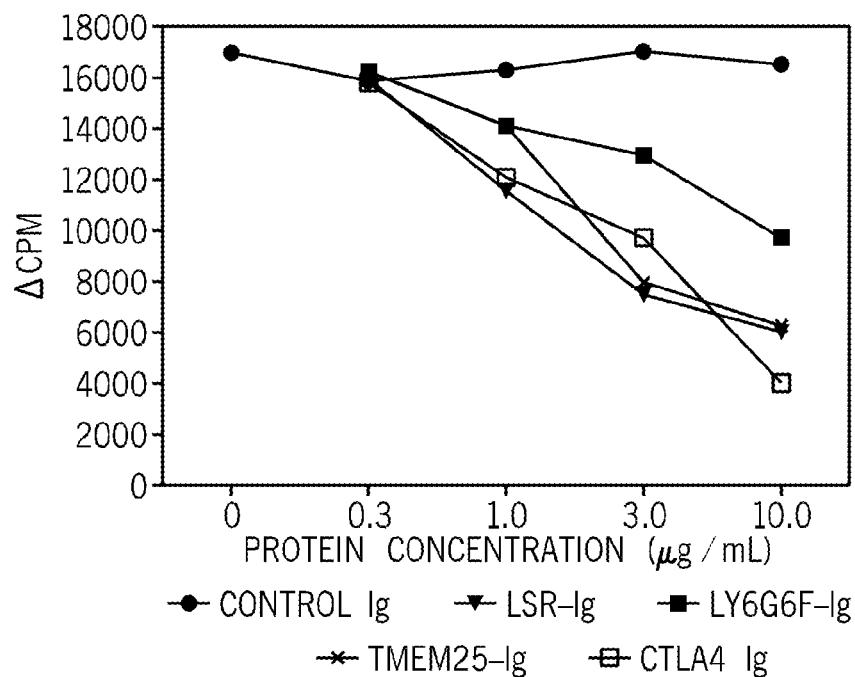


FIG. 30E

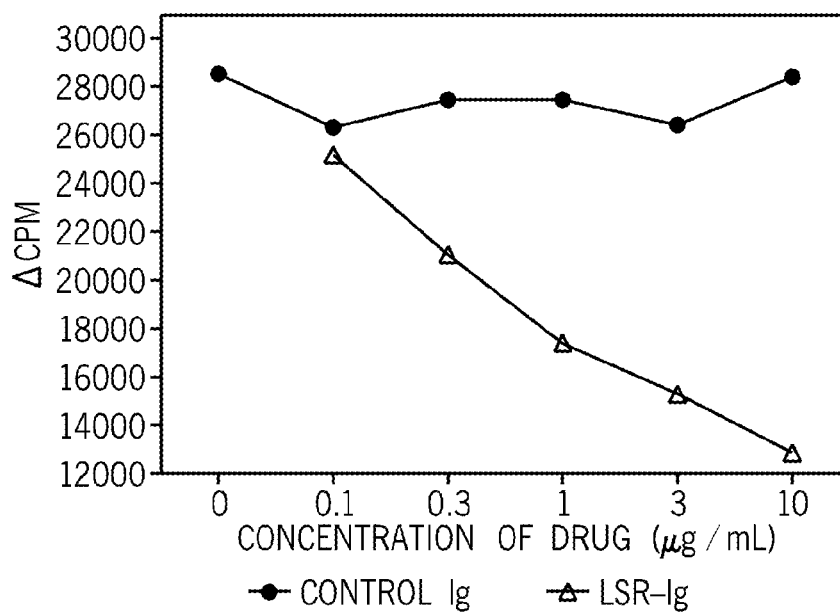


FIG. 31

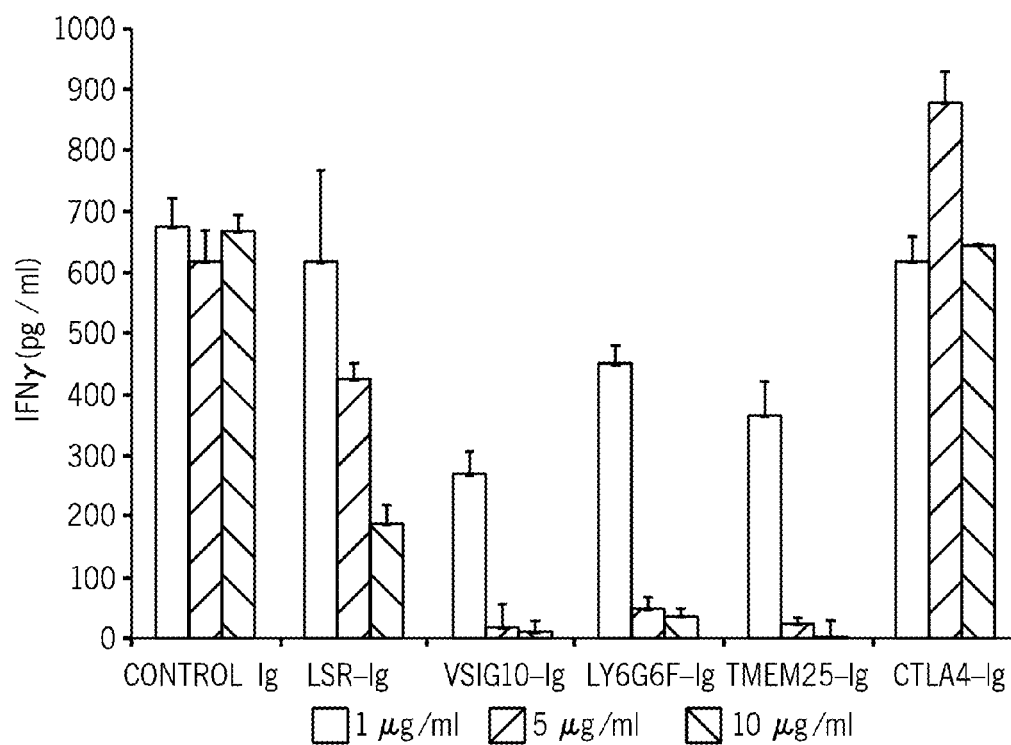


FIG. 32A

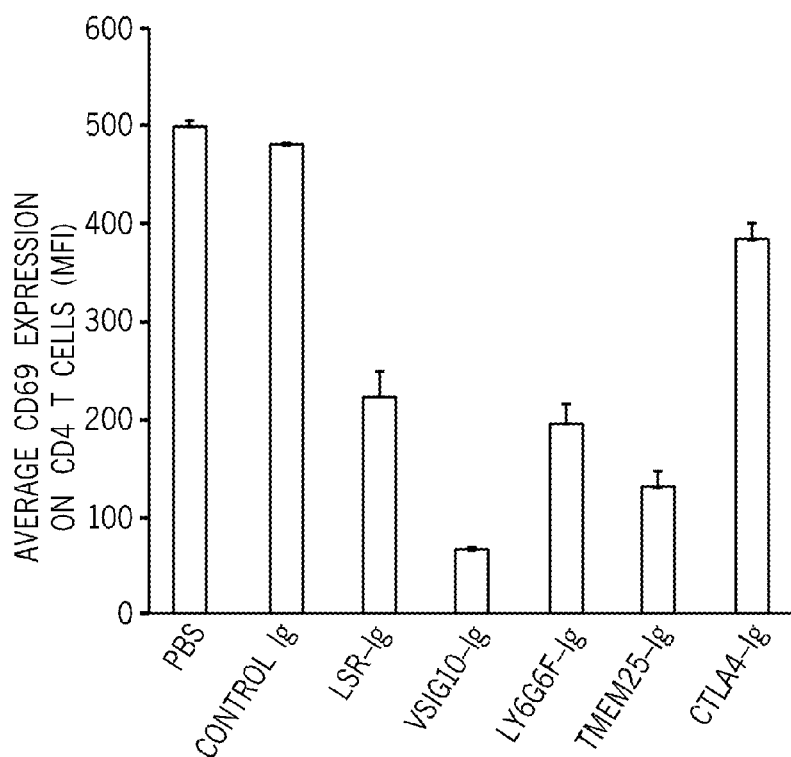


FIG. 32B

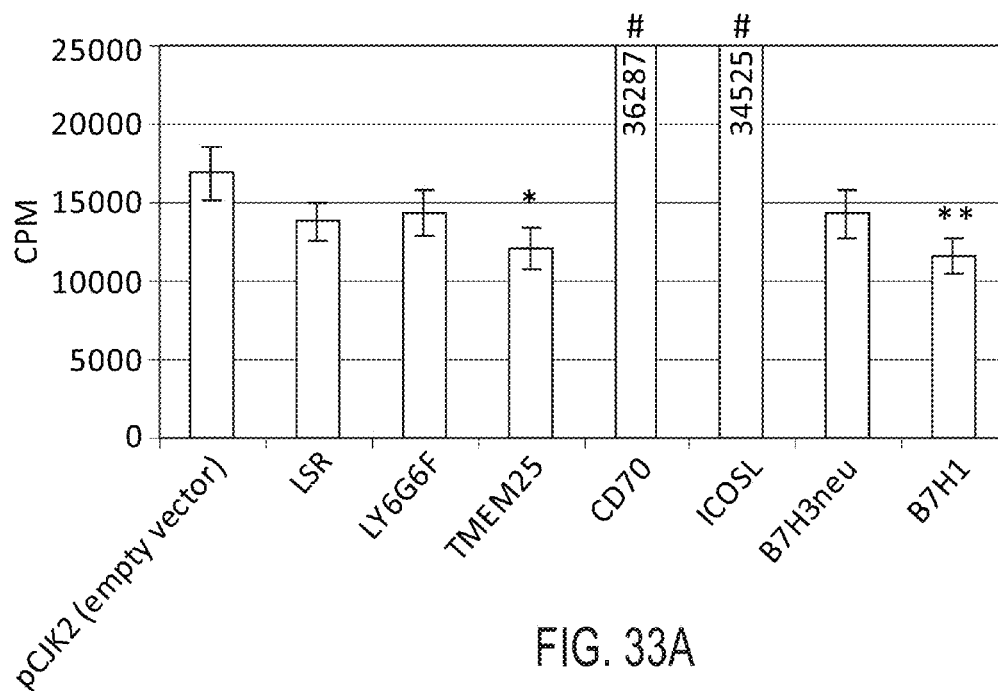


FIG. 33A

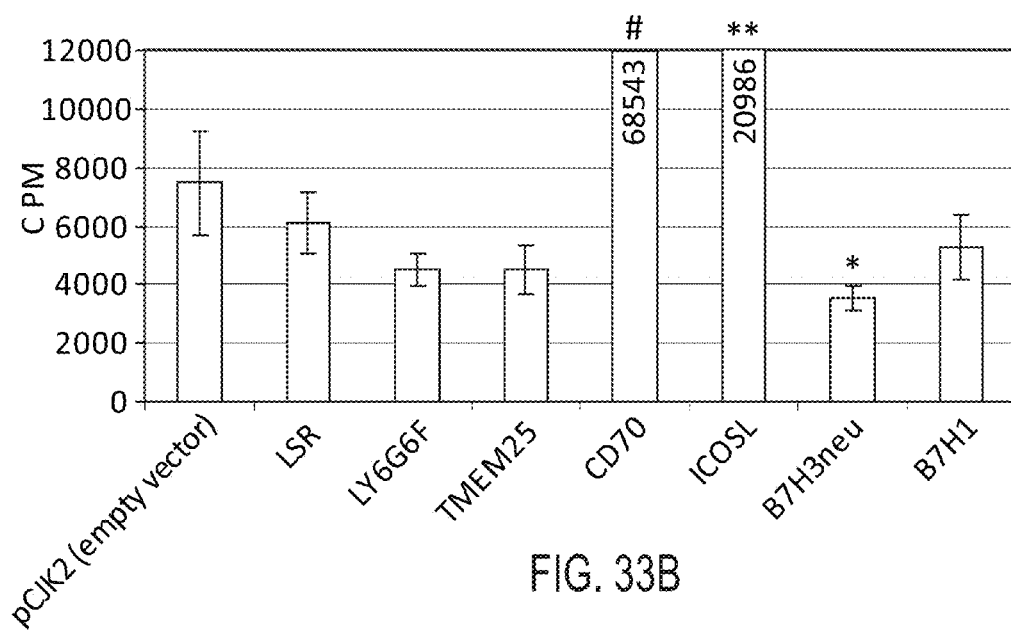


FIG. 33B

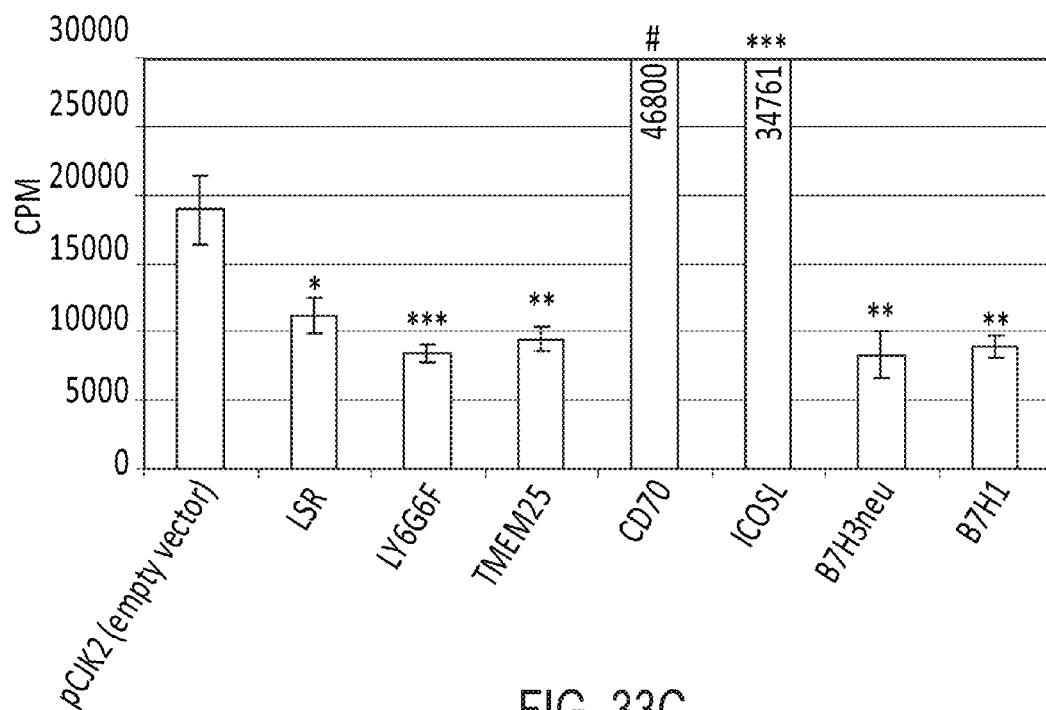


FIG. 33C

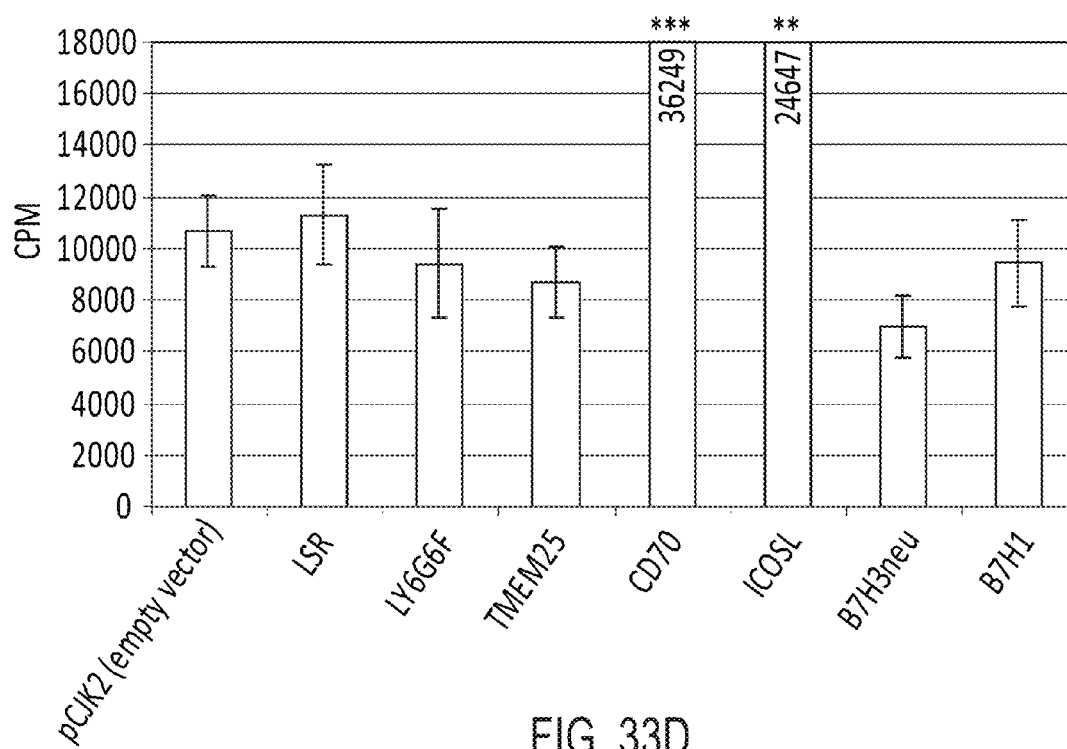
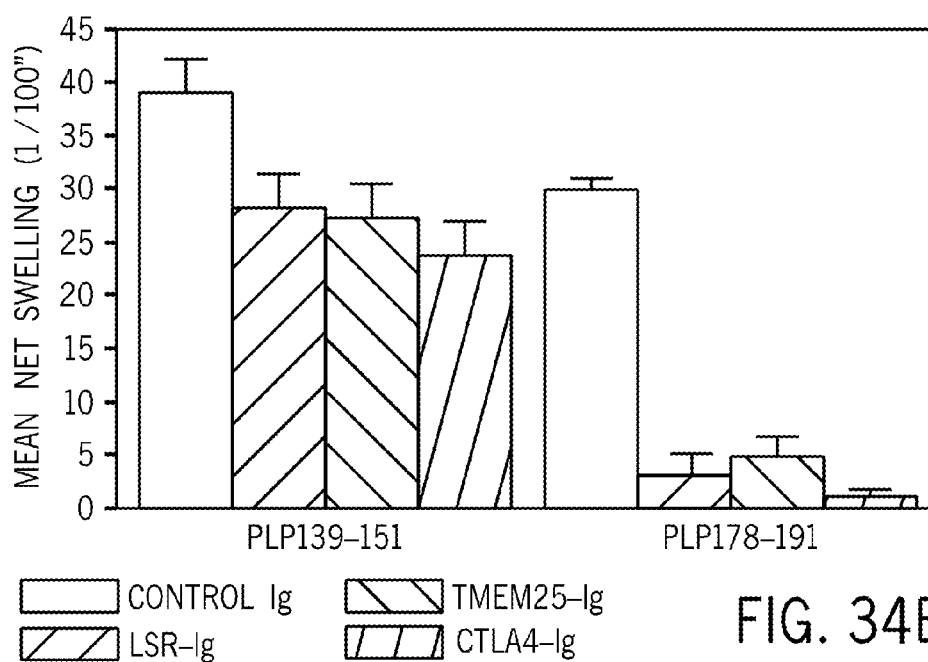
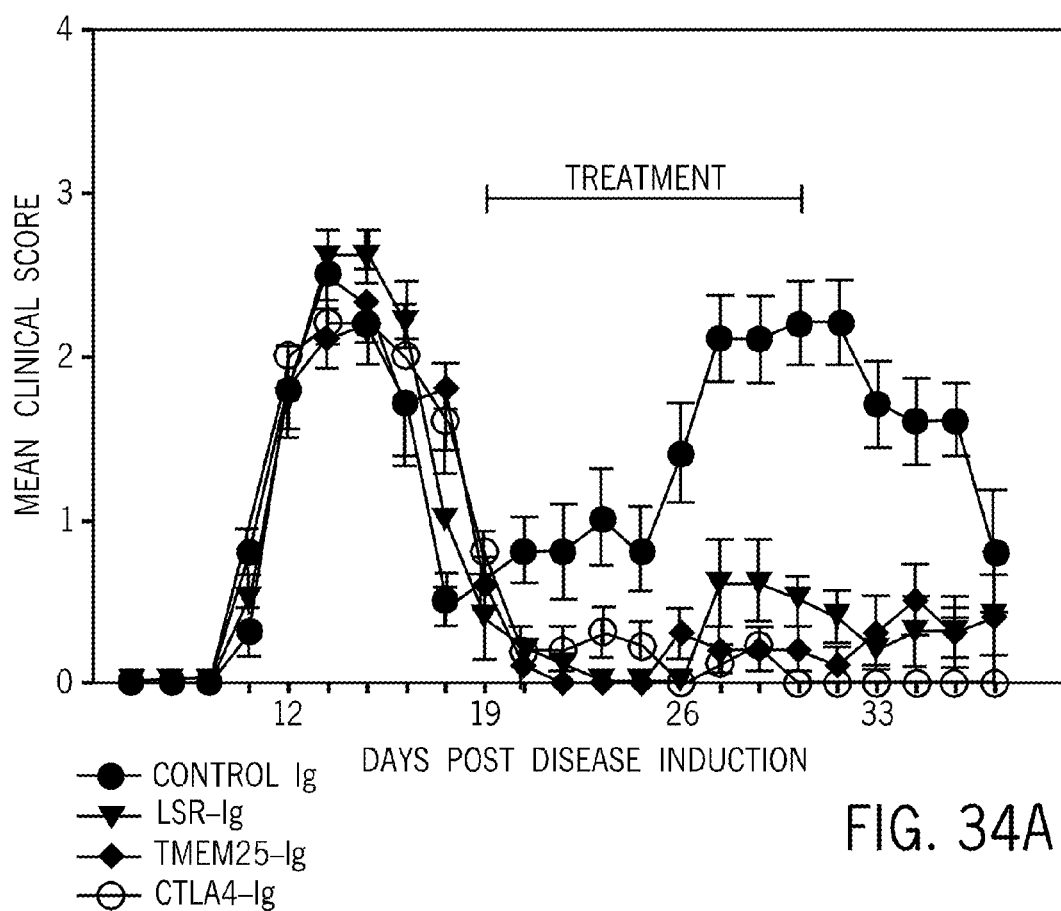


FIG. 33D



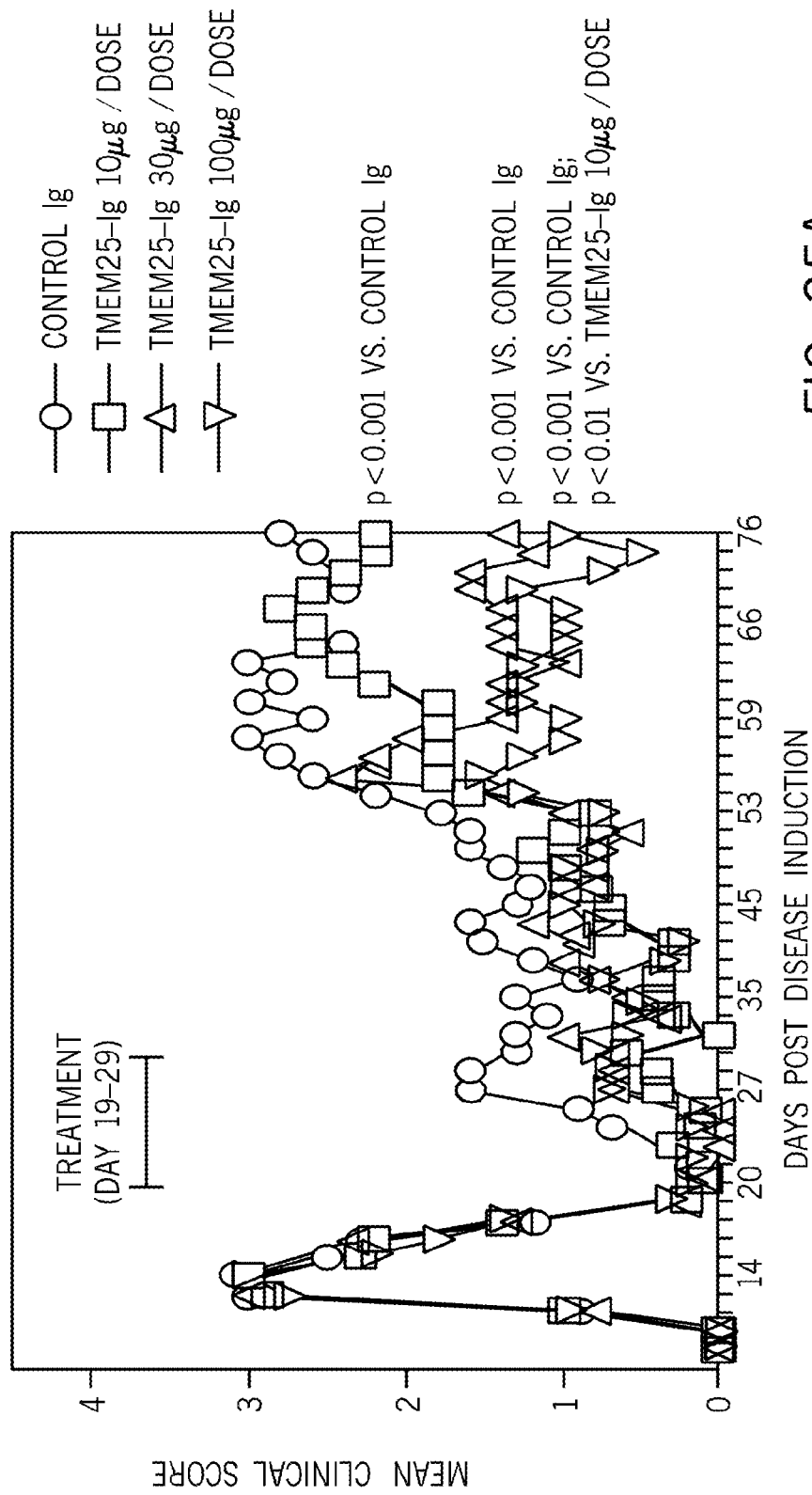


FIG. 35A

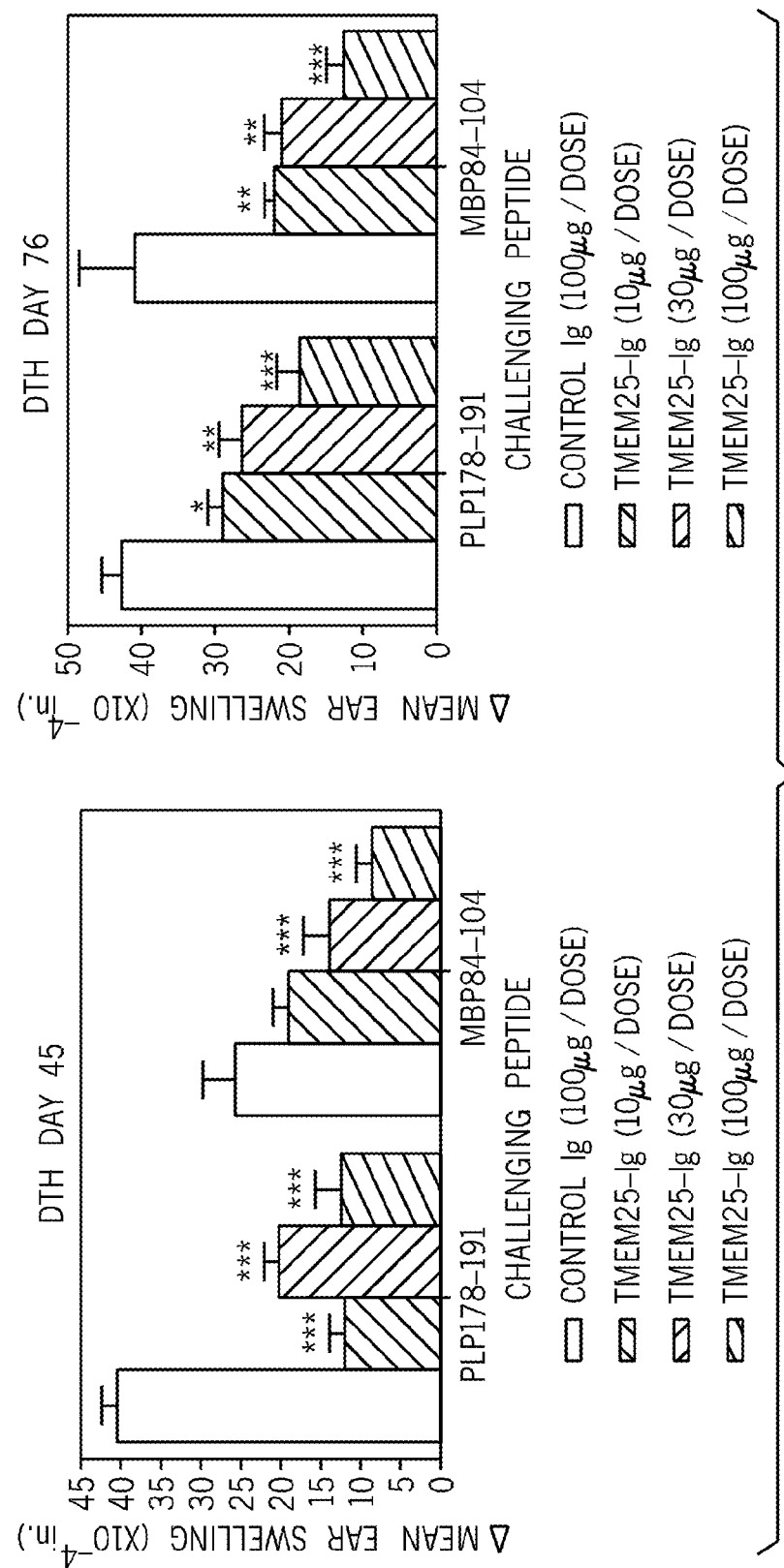


FIG. 35B

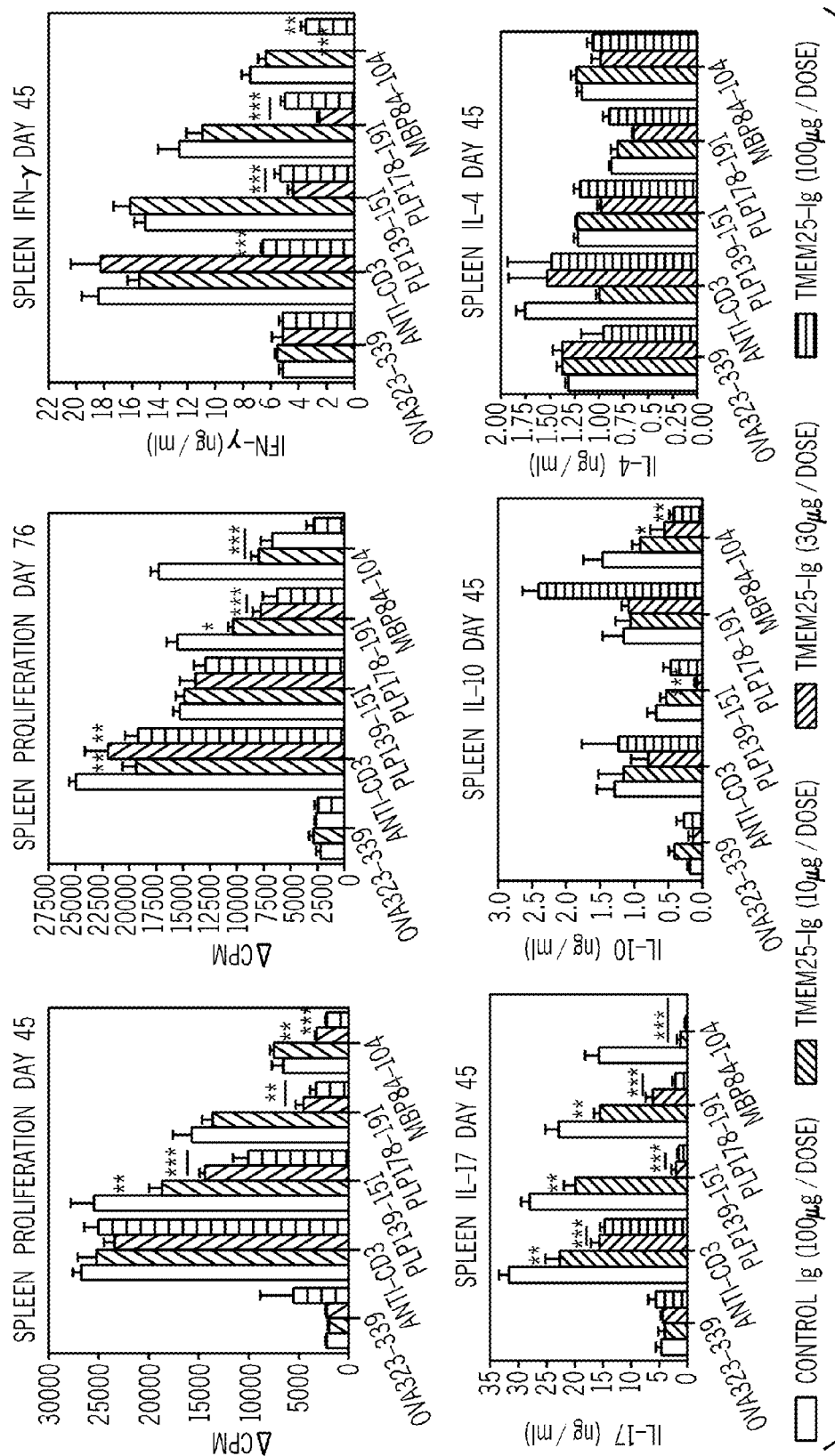


FIG. 35C

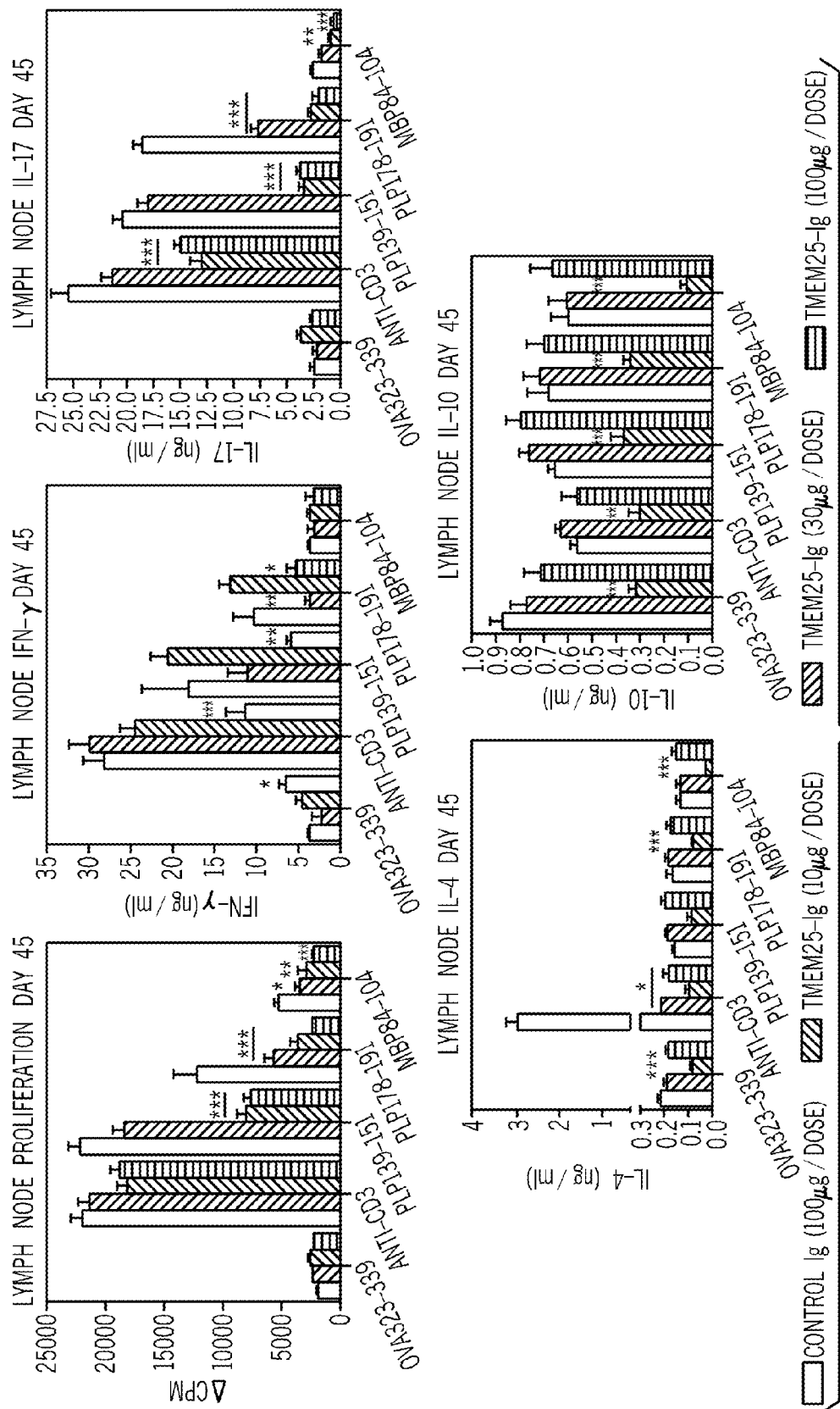


FIG. 35D

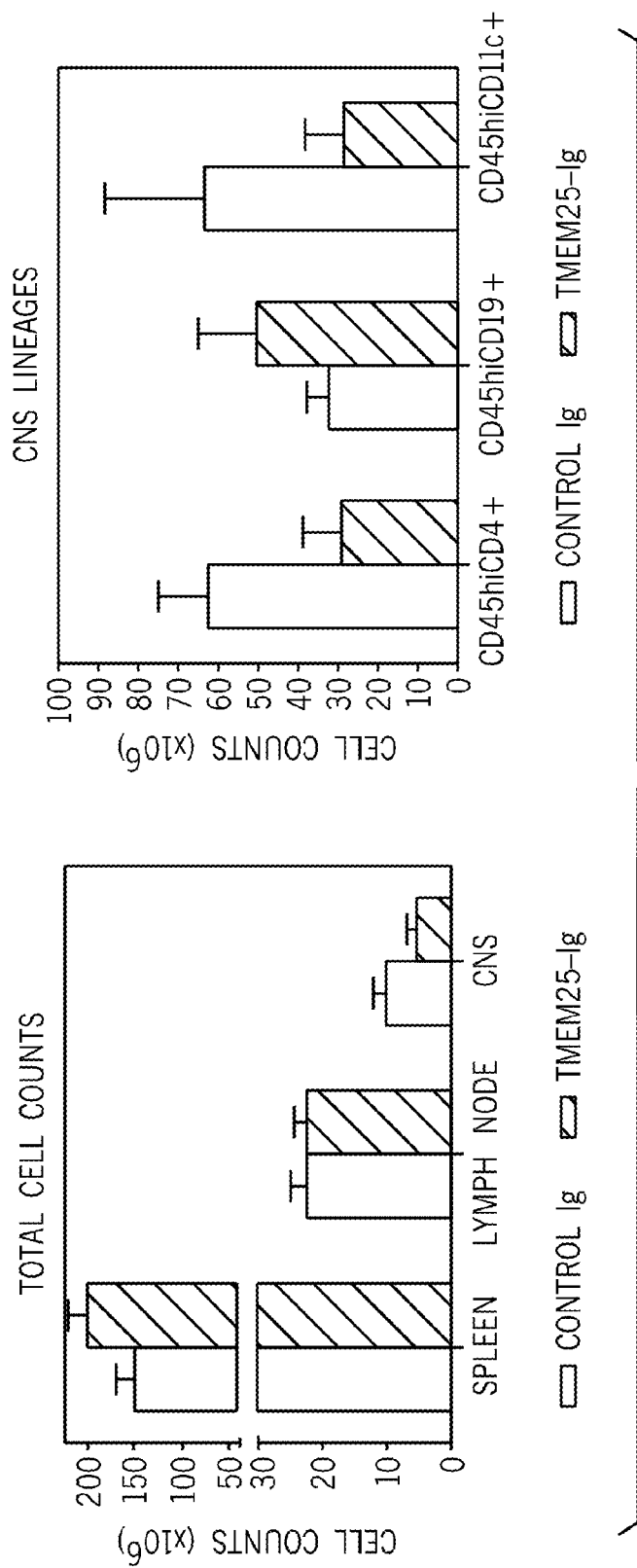


FIG. 35E

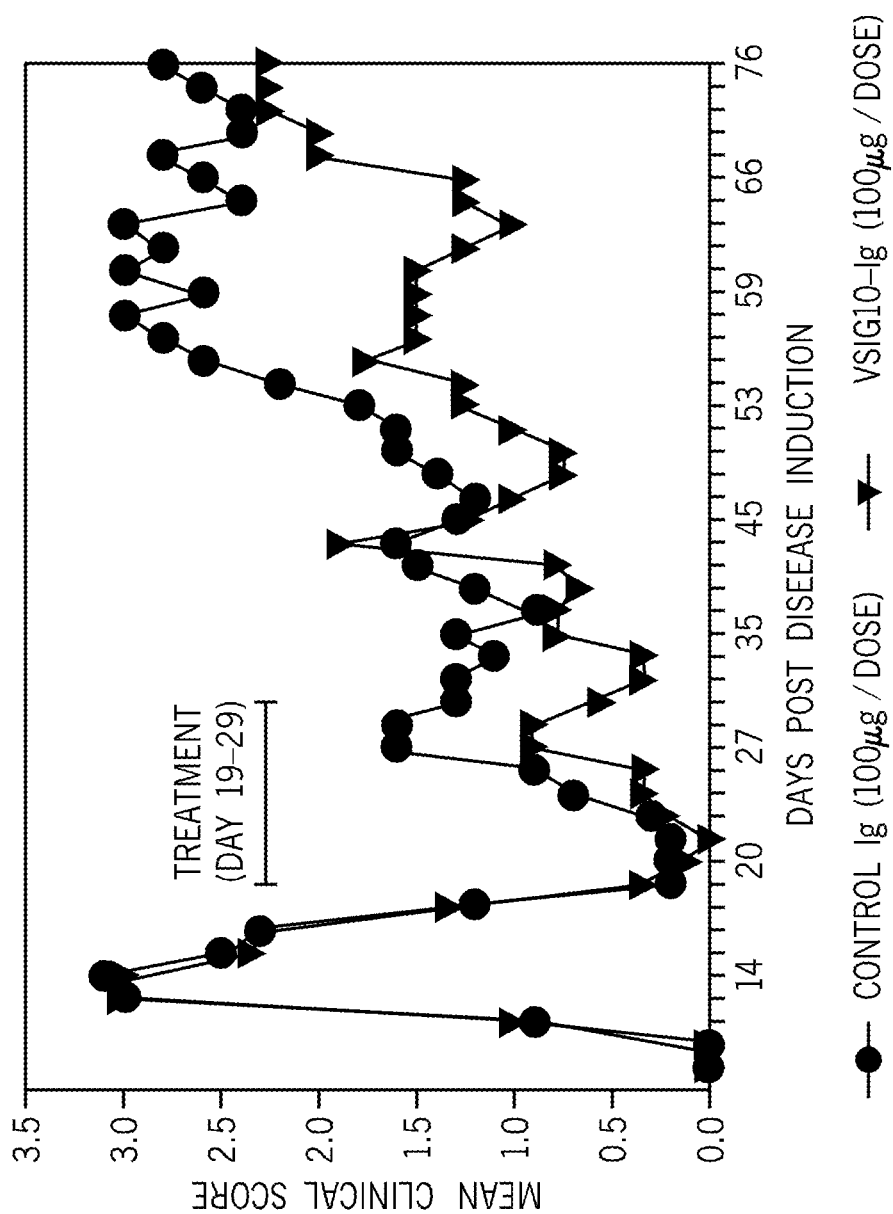


FIG. 36A

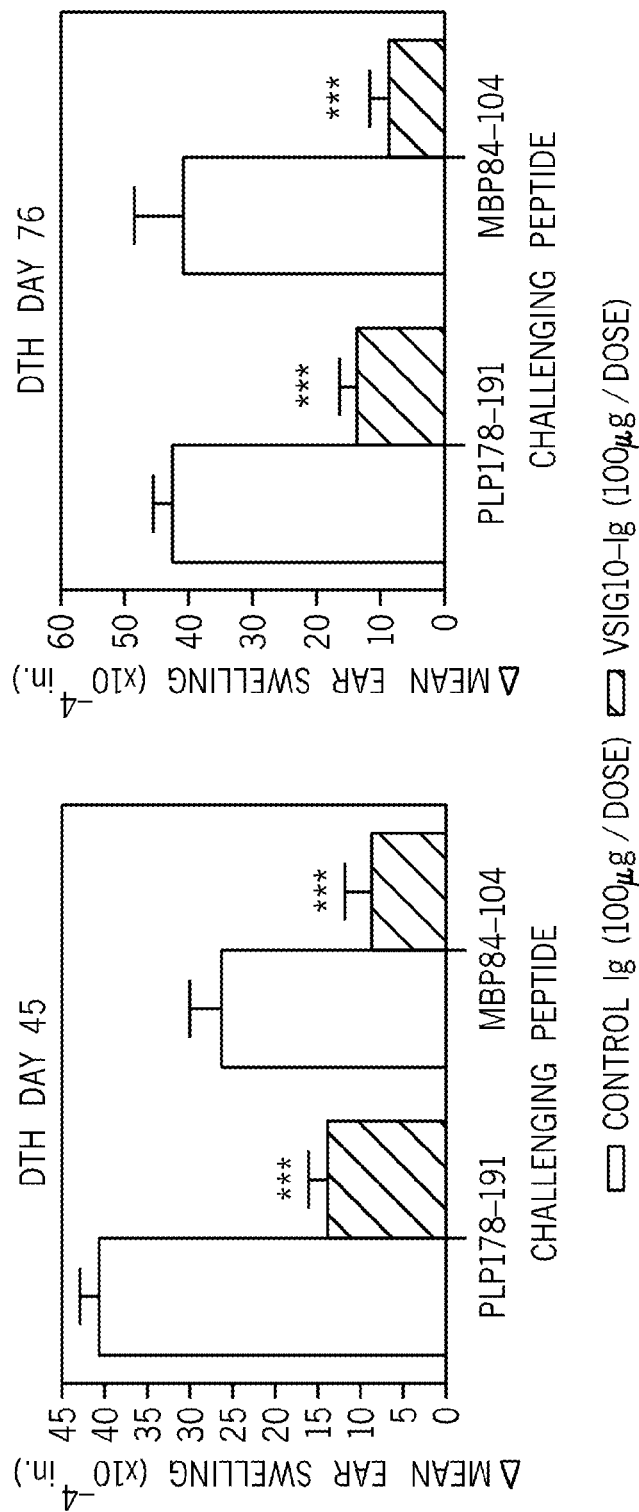


FIG. 36B

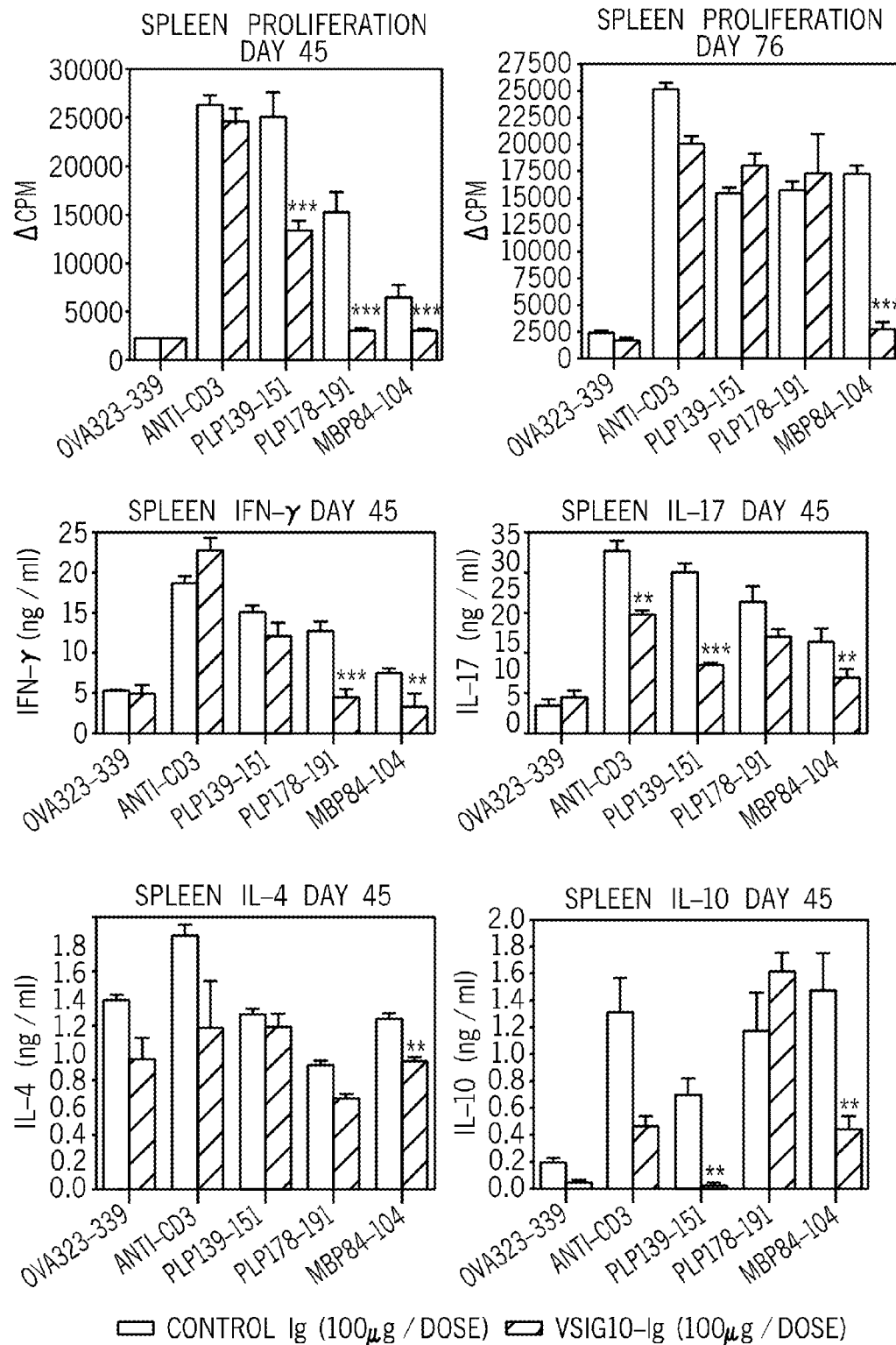


FIG. 36C

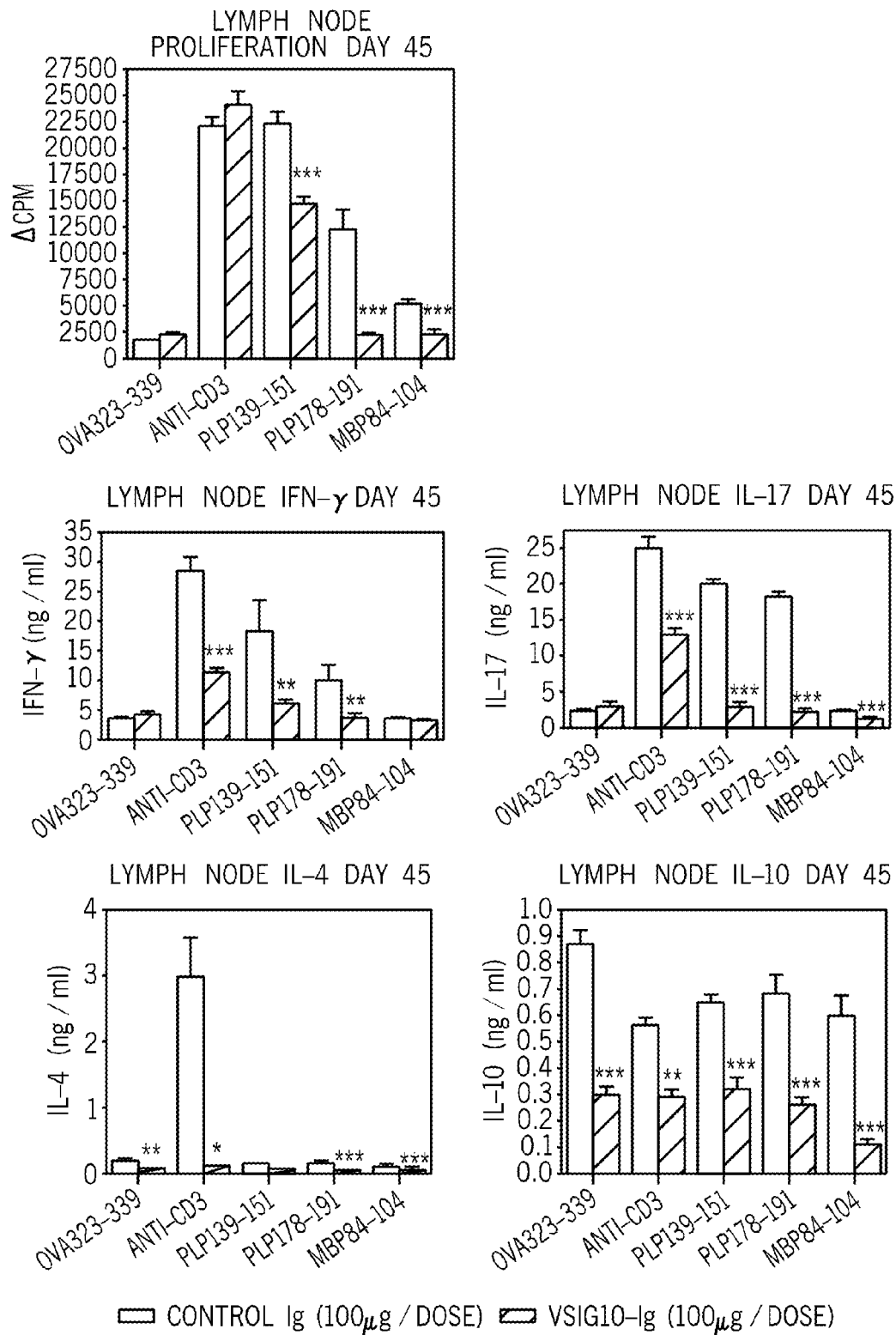


FIG. 36D

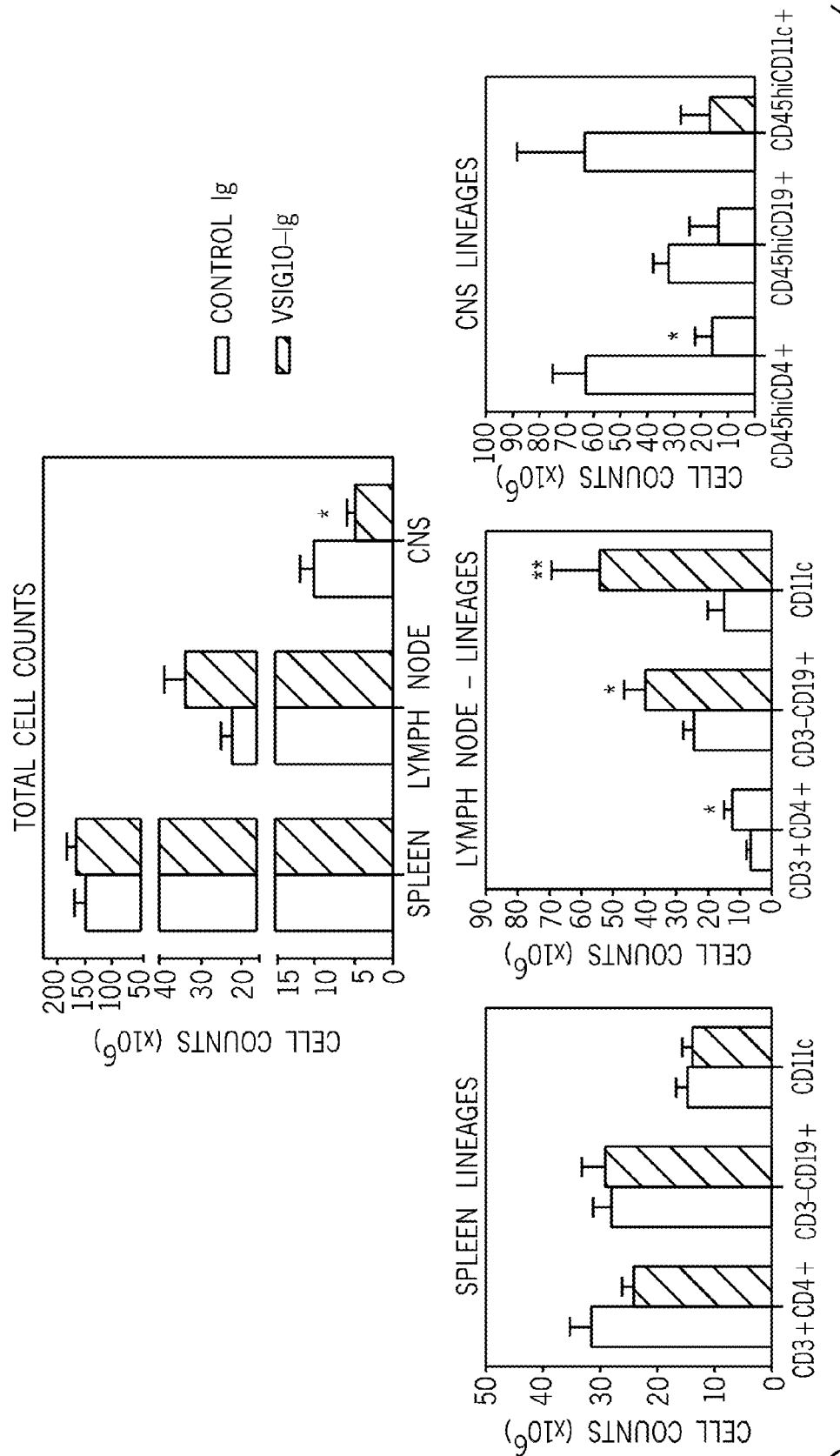


FIG. 36E

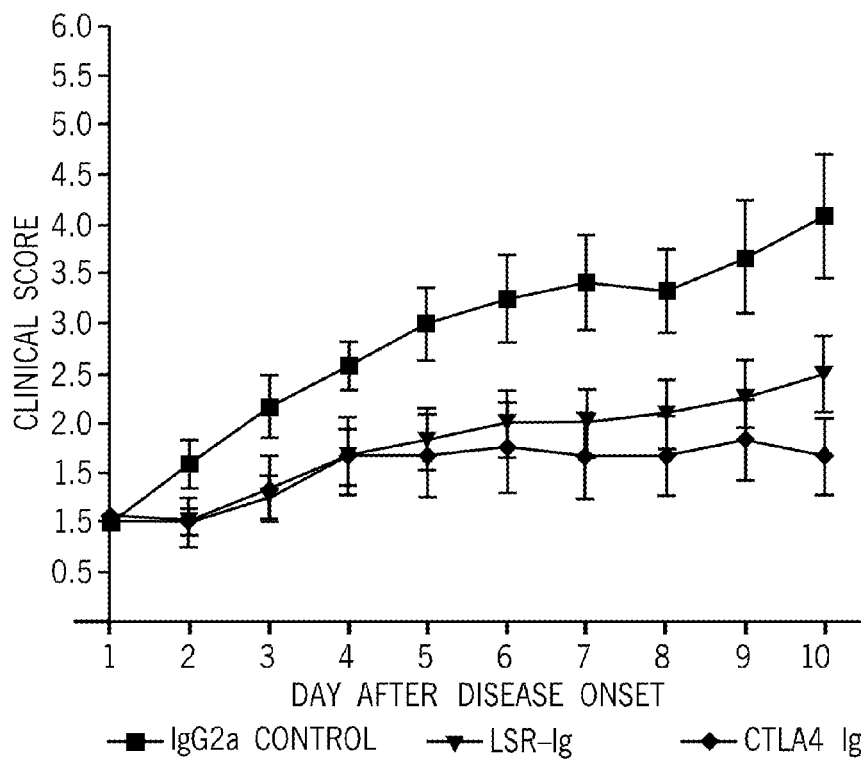


FIG. 37A

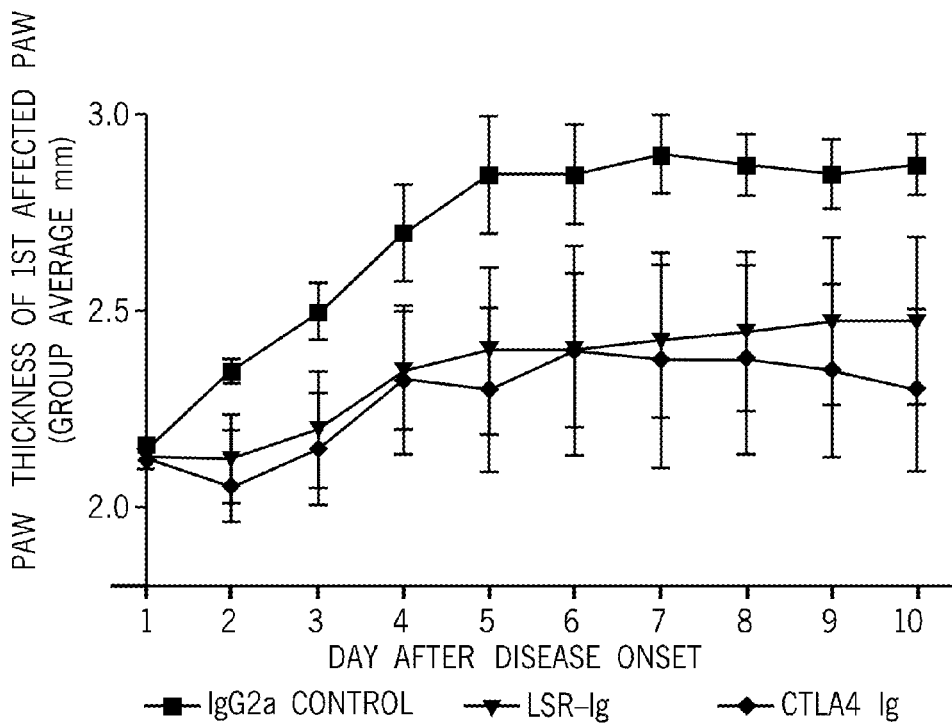


FIG. 37B

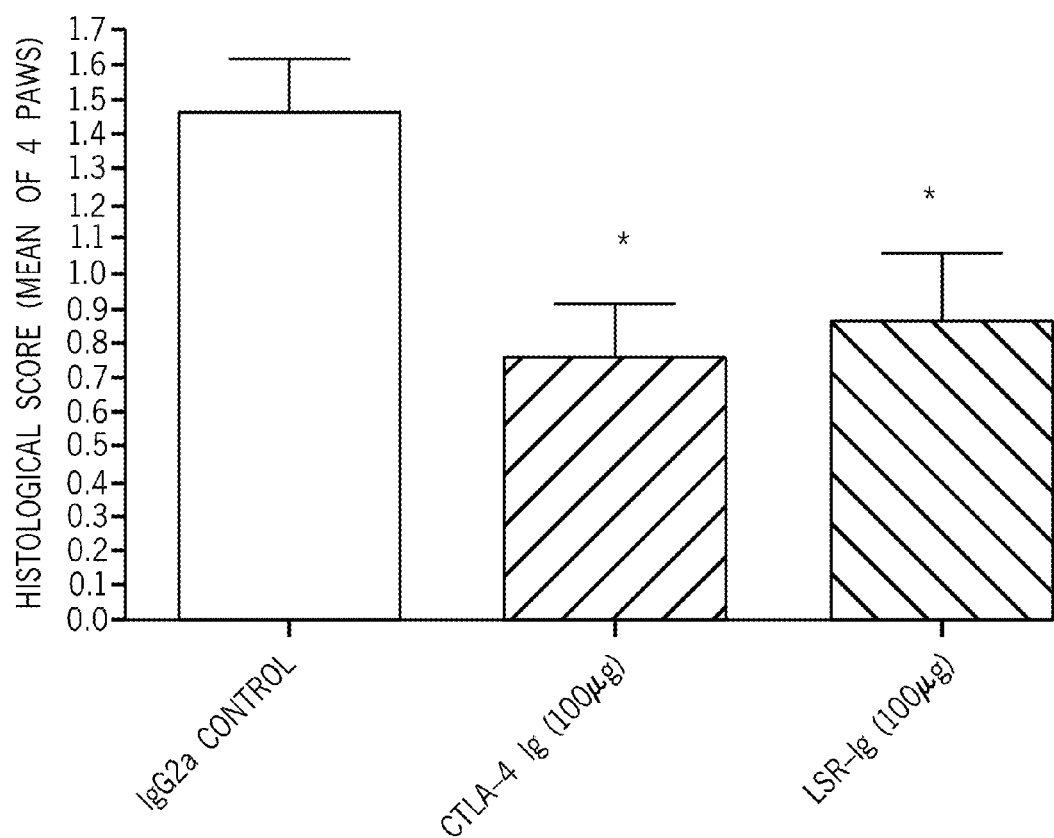


FIG. 37C

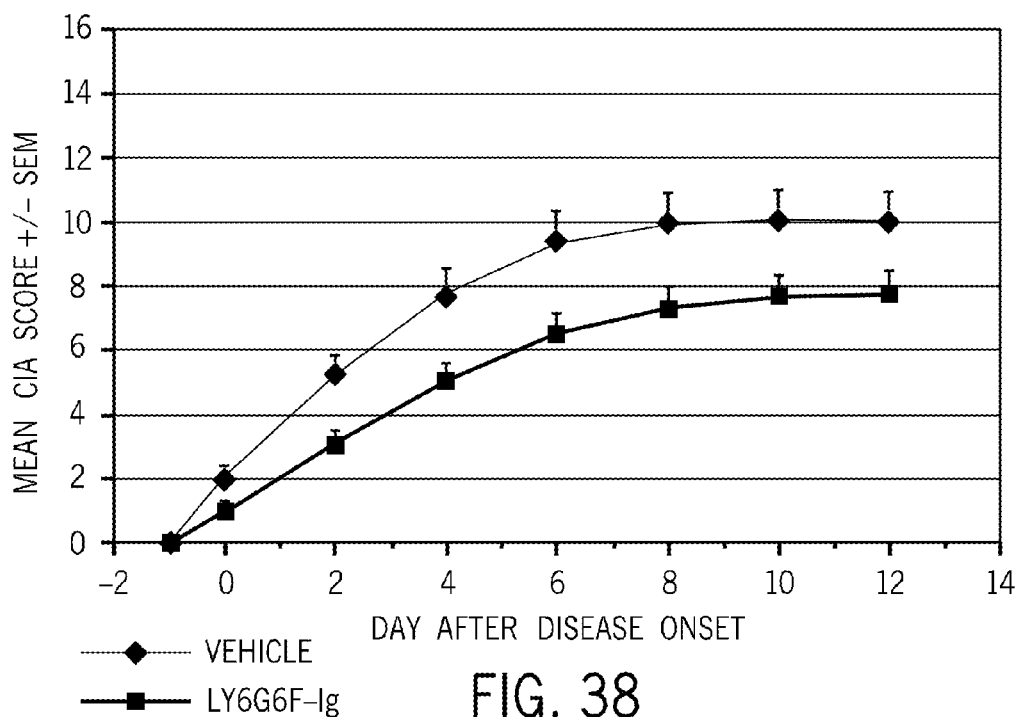


FIG. 38

1

POLYPEPTIDES AND POLYNUCLEOTIDES, AND USES THEREOF FOR TREATMENT OF IMMUNE RELATED DISORDERS AND CANCER

REFERENCE TO SEQUENCE LISTING

The Sequence Listing is filed herewith electronically as a separate ASCII file entitled "2585-seq-listing.txt", created on Apr. 16 2012, having 427000 bytes in size; the contents of which are hereby incorporated by reference as if fully set forth herein.

FIELD OF THE INVENTION

This invention relates to LY6G6F, VSIG10, TMEM25 and LSR proteins, which are suitable targets for immunotherapy, treatment of cancer, infectious disorders, and/or immune related disorders, and drug development, as well as soluble molecules and conjugates thereof, and antibodies against such.

BACKGROUND OF THE INVENTION

Naïve T cells must receive two independent signals from antigen-presenting cells (APC) in order to become productively activated. The first, Signal 1, is antigen-specific and occurs when T cell antigen receptors encounter the appropriate antigen-MHC complex on the APC. The fate of the immune response is determined by a second, antigen-independent signal (Signal 2) which is delivered through a T cell costimulatory molecule that engages its APC-expressed ligand. This second signal could be either stimulatory (positive costimulation) or inhibitory (negative costimulation or coinhibition). In the absence of a costimulatory signal, or in the presence of a coinhibitory signal, T-cell activation is impaired or aborted, which may lead to a state of antigen-specific unresponsiveness (known as T-cell anergy), or may result in T-cell apoptotic death.

Costimulatory molecule pairs usually consist of ligands expressed on APCs and their cognate receptors expressed on T cells. The prototype ligand/receptor pairs of costimulatory molecules are B7/CD28 and CD40/CD40L. The B7 family consists of structurally related, cell-surface protein ligands, which may provide stimulatory or inhibitory input to an immune response. Members of the B7 family are structurally related, with the extracellular domain containing at least one variable or constant immunoglobulin domain.

Both positive and negative costimulatory signals play critical roles in the regulation of cell-mediated immune responses, and molecules that mediate these signals have proven to be effective targets for immunomodulation. Based on this knowledge, several therapeutic approaches that involve targeting of costimulatory molecules have been developed, and were shown to be useful for prevention and treatment of cancer by turning on, or preventing the turning off, of immune responses in cancer patients and for prevention and treatment of autoimmune diseases and inflammatory diseases, as well as rejection of allogeneic transplantation, each by turning off uncontrolled immune responses, or by induction of "off signal" by negative costimulation (or coinhibition) in subjects with these pathological conditions.

Manipulation of the signals delivered by B7 ligands has shown potential in the treatment of autoimmunity, inflammatory diseases, and transplant rejection. Therapeutic strategies include blocking of costimulation using monoclonal antibodies to the ligand or to the receptor of a costimulatory pair, or

2

using soluble fusion proteins composed of the costimulatory receptor that may bind and block its appropriate ligand. Another approach is induction of co-inhibition using soluble fusion protein of an inhibitory ligand. These approaches rely, at least partially, on the eventual deletion of auto- or allo-reactive T cells (which are responsible for the pathogenic processes in autoimmune diseases or transplantation, respectively), presumably because in the absence of costimulation (which induces cell survival genes) T cells become highly susceptible to induction of apoptosis. Thus, novel agents that are capable of modulating costimulatory signals, without compromising the immune system's ability to defend against pathogens, are highly advantageous for treatment and prevention of such pathological conditions.

Costimulatory pathways play an important role in tumor development. Interestingly, tumors have been shown to evade immune destruction by impeding T cell activation through inhibition of co-stimulatory factors in the B7-CD28 and TNF families, as well as by attracting regulatory T cells, which inhibit anti-tumor T cell responses (see Wang (2006) Immune Suppression by Tumor Specific CD4+ Regulatory T cells in Cancer. *Semin Cancer Biol.* 16:73-79; Greenwald, et al. (2005) The B7 Family Revisited. *Ann. Rev. Immunol.* 23:515-48; Watts (2005) TNF/TNFR Family Members in Co-stimulation of T Cell Responses *Ann. Rev. Immunol.* 23:23-68; Sadum, et al. (2007) Immune Signatures of Murine and Human Cancers Reveal Unique Mechanisms of Tumor Escape and New Targets for Cancer Immunotherapy. *Clin. Cane. Res.* 13(13): 4016-4025). Such tumor expressed costimulatory molecules have become attractive cancer biomarkers and may serve as tumor-associated antigens (TAAs). Furthermore, costimulatory pathways have been identified as immunologic checkpoints that attenuate T cell dependent immune responses, both at the level of initiation and effector function within tumor metastases. As engineered cancer vaccines continue to improve, it is becoming clear that such immunologic checkpoints are a major barrier to the vaccines' ability to induce therapeutic anti-tumor responses. In that regard, costimulatory molecules can serve as adjuvants for active (vaccination) and passive (antibody-mediated) cancer immunotherapy, providing strategies to thwart immune tolerance and stimulate the immune system.

In addition, such agents could be of use in other types of cancer immunotherapy, such as adoptive immunotherapy, in which tumor-specific T cell populations are expanded and directed to attack and kill tumor cells. Agents capable of augmenting such anti-tumor response have great therapeutic potential and may be of value in the attempt to overcome the obstacles to tumor immunotherapy. Recently, novel agents that modulate several costimulatory pathways were indeed introduced to the clinic as cancer immunotherapy.

Emerging data from a wide range of studies on acute and chronic infections support an important role for negative costimulatory receptors also in controlling infection. Memory CD8 T cells generated after an acute viral infection are highly functional and constitute an important component of protective immunity. Modulation of costimulatory pathway has also been proven effective in optimizing antiviral immunity by limiting the memory T cell response to its protective capacities (Teijaro et al., *J Immunol.* 2009: 182; 5430-5438). This has been demonstrated in models of influenza infection in which inhibiting CD28 costimulation with CTLA4-Ig suppressed primary immune responses in naive mice infected with influenza, but was remarkably curative for memory CD4 T cell-mediated secondary responses to influenza leading to improved clinical outcome and increased survival to influenza challenge.

Chronic infections are often characterized by varying degrees of functional impairment of virus-specific T-cell responses, and this defect is a principal reason for the inability of the host to eliminate the persisting pathogen. Although functional effector T cells are initially generated during the early stages of infection, they gradually lose function during the course of the chronic infection as a result of persistent exposure to foreign antigen, giving rise to T cell exhaustion. Exhausted T cells express high levels of multiple co-inhibitory receptors such as CTLA-4, PD-1, and LAG3 (Crawford et al., *Curr Opin Immunol.* 2009; 21:179-186; Kaufmann et al., *J Immunol* 2009; 182:5891-5897, Sharpe et al., *Nat Immunol* 2007; 8:239-245). PD-1 overexpression by exhausted T cells was observed clinically in patients suffering from chronic viral infections including HIV, HCV and HBV (Crawford et al., *Curr Opin Immunol* 2009; 21:179-186; Kaufmann et al., *J Immunol* 2009; 182:5891-5897, Sharpe et al., *Nat Immunol* 2007; 8:239-245). There has been some investigation into this pathway in additional pathogens, including other viruses, bacteria, and parasites (Hofmeyer et al., *J Biomed Biotechnol.* Vol 2011, Art. ID 451694, Bhadra et al., *Proc Natl Acad. Sci.* 2011; 108(22):9196-201). For example, the PD-1 pathway was shown to be involved in controlling bacterial infection using a sepsis model induced by the standard cecal ligation and puncture method. The absence of PD-1 in knockout mice protected from sepsis-induced death in this model (Huang et al., *PNAS* 2009; 106: 6303-6308).

T cell exhaustion can be reversed by blocking co-inhibitory pathways such as PD-1 or CTLA-4 (Rivas et al., *J Immunol.* 2009; 183:4284-91; Golden-Mason et al., *J Virol.* 2009; 83:9122-30; Hofmeyer et al., *J Biomed Biotechnol.* Vol 2011, Art. ID 451694), thus allowing restoration of anti viral immune function. The therapeutic potential of co-inhibition blockade for treating viral infection was extensively studied by blocking the PD-1/PD-L1 pathway, which was shown to be efficacious in several animal models of infection including acute and chronic simian immunodeficiency virus (SIV) infection in rhesus macaques (Valu et al., *Nature* 2009; 458: 206-210) and in mouse models of chronic viral infection, such as lymphocytic choriomeningitis virus (LCMV) (Barber et al., *Nature.* 2006; 439:682-7), and Theiler's murine encephalomyelitis virus (TMEV) model in SJL/J mice (Duncan and Miller *PLoS One.* 2011; 6:e18548). In these models PD-1/PD-L1 blockade improved anti viral responses and promoted clearance of the persisting viruses. In addition, PD-1/PD-L1 blockade increased the humoral immunity manifested as elevated production of specific anti-virus antibodies in the plasma, which in combination with the improved cellular responses leads to decrease in plasma viral loads and increased survival.

Blocking negative signaling pathways, such as PD-1 and CTLA-4, can restore the host immune system, enabling it to respond to further stimulation. Combining therapeutic vaccination along with the blockade of inhibitory signals could synergistically enhance functional CD8 T-cell responses and improve viral control in chronically infected individuals, providing a promising strategy for the treatment of chronic viral infections, such as human immunodeficiency virus, hepatitis B virus, and hepatitis C virus (Ha et al, *Immunol Rev.* 2008 June; 223:317-33). The results of a recent study indicate that blocking of the PD-1 pathway improved T cell responses to HBV vaccination in subjects with HCV infection, and raise the possibility that blocking this pathway might improve success rates of immunization in the setting of chronic viral infection (Moorman et al, *Vaccine.* 2011 Apr. 12; 29(17): 3169-76). Antibodies to PD-1 and CTLA-4 are currently in

clinical trials in chronic hepatitis C, as promising candidates for combination with both prophylactic and therapeutic vaccines (Diepolder and Obst, *Expert Rev Vaccines.* 2010 March; 9(3):243-7). PD-1 blockade also enhances the effectiveness of prophylactic vaccination leading to an increase in epitope specific T cells (Finnefrock et al., *J Immunol* 2009; 182; 980-987).

In addition to blockade of co-inhibitory pathways for treatment of chronic infections, recent studies using viral infection models have highlighted the importance of positive costimulatory signals during memory responses against viruses. Costimulatory molecules such as CD28, 4-1BB, and OX40 have also been implicated in the survival, generation, maintenance, and quality of virus-specific memory CD8+ T cells. The delivery of costimulatory signals can help boost the generation and function of virus-specific memory CD8+ T cells. The use of costimulatory molecules as adjuvants, along with viral antigens in vaccines, may facilitate the generation of effective antigen-specific memory CD8+ T-cell responses, and may therefore lead to improved vaccines (Duttagupta et al, *Crit Rev Immunol.* 2009; 29(6):469-86).

A recent study also evaluated the effects of soluble PD-1 (sPD-1) as a blockade of PD-1 and PD-L1 on vaccine-elicited antigen-specific T-cell responses in mice. Coadministration of sPD-1 with a DNA vaccine or with an adenovirus-based vaccine, increased antigen-specific CD8(+) T-cell responses, indicating vaccine type-independent adjuvant effect of sPD-1 (Song et al, *J Immunother.* 2011 April; 34(3):297-306). These and additional results of this study suggest that an immunization strategy using the soluble extracellular domain (ECD) of a negative costimulatory protein as an adjuvant, could be used to increase antigen-specific T-cell immunity elicited by vaccination.

B cells have also long been considered to have a key role in the development and maintenance of many autoimmune diseases through production of pathogenic autoantibodies, such as systemic lupus erythematosus (SLE) and Sjogren's disease. However, it is clear that a number of other B cell functions are also critical in the pathogenesis of organ-specific autoimmune diseases that were previously thought to be mainly T cell mediated, such as rheumatoid arthritis (RA) and type 1 diabetes (T1D) (Wong et al 2010, *Curr Opin Immunol.* 22:723-731).

T cell help to B cells is a pivotal process of adaptive immune responses. Follicular helper T (T_{fh}) cells are a subset of CD4+ T cells specialized in B cell help (reviewed by Crotty, *Annu. Rev. Immunol.* 29: 621-663, 2011). T_{fh} cells express the B cell homing chemokine receptor, CXCR5, which drives T_{fh} cell migration into B cell follicles within lymph nodes in a CXCL13-dependent manner. T_{fh} cells first interact with cognate B cells at the T cell-B cell border and subsequently induce germinal center B cell differentiation and germinal center formation within the follicle (Reviewed by Crotty, *Annu. Rev. Immunol.* 29: 621-663, 2011). The requirement of T_{fh} cells for B cell help and T cell-dependent antibody responses indicates that this cell type is of great importance for protective immunity against various types of infectious agents, as well as for rational vaccine design. Not surprisingly, dysregulation and aberrant accumulation of T_{fh} cells has also been linked with autoimmune diseases, such as Sjogren's disease and autoimmune arthritis (Yu and Vinuesa, 2010, *Cell. Mol. Immunol.* 7: 198-203).

T_{fh} cells selectively express a wealth of surface proteins, which are involved in their selective localization (such as CXCR5) and in direct physical interactions with B cells to provide B cell help. Among the latter group are several members of the costimulatory proteins family which are highly

expressed in Tfh cells, including the inducible co-stimulatory receptor ICOS, and the negative costimulators (inhibitory receptors) PD-1 and BTLA (Crotty, *Annu. Rev. Immunol.* 29: 621-663, 2011), thus this cell subset may be also controlled by modulation of costimulatory and coinhibitory pathways, contributing to the effect on B cell function.

Regulating costimulation using agonists and/or antagonists to various costimulatory proteins has been extensively studied as a strategy for treating autoimmune diseases, graft rejection, allergy and cancer. This field has been clinically pioneered by CTLA4-Ig (Abatacept, Orencia®) which is approved for treatment of RA, mutated CTLA4-Ig (Belatacept, Nulojix®) for prevention of acute kidney transplant rejection and by the anti-CTLA4 antibody (Ipilimumab, Yervoy®), recently approved for the treatment of melanoma. Other costimulation regulators are currently in advanced stages of clinical development including anti-PD-1 antibody (MDX-1106) which is in development for treatment of advanced/metastatic clear-cell renal cell carcinoma (RCC) and anti-CD40L Antibody (BG9588, Antova®) for treatment of renal allograft transplantation. Furthermore, such agents are also in clinical development for viral infections, for example the anti PD-1 Ab, MDX-1106, which is being tested for treatment of hepatitis C, and the anti-CTLA-4 Ab CP-675, 206 (tremelimumab) which is in a clinical trial in hepatitis C virus-infected patients with hepatocellular carcinoma; the goals of the study are to test its effect on the carcinoma and on the replication of the virus.

BRIEF SUMMARY OF THE INVENTION

According to at least some embodiments, the invention provides novel therapeutic and diagnostic compositions containing an ectodomain or soluble or secreted form of the LY6G6F, VSIG10, TMEM25 and/or LSR proteins and/or variants and/or orthologs and/or fragments, and/or conjugate containing same, and/or nucleic acid sequences encoding for same.

The full length amino acid sequence of the known (wild type) LY6G6F protein (lymphocyte antigen 6 complex locus protein G6f, genbank accession number: NP_001003693, SEQ ID NO:1) is shown in FIG. 1A. The full length amino acid sequence of known (wild type) VSIG10 protein (V-set and immunoglobulin domain-containing protein 10, genbank accession number: NP_061959, SEQ ID NO:3), and the amino acid sequence of VSIG10 novel variant (SEQ ID NO:5) are shown in FIGS. 1B and 1C, respectively. The amino acid sequence alignment of VSIG10 novel variant (SEQ ID NO:5) and the known (wild type) VSIG10 protein (SEQ ID NO:3) is shown in FIG. 2A. The full length amino acid sequence of known (wild type) TMEM25 protein (Transmembrane protein 25, Swiss-Prot accession number: Q86YD3, SEQ ID NO:7) is shown in FIG. 1D. The full length amino acid sequence of known (wild type) LSR protein (lipolysis-stimulated lipoprotein receptor isoform 2, genbank accession number: NP_991403) is provided in SEQ ID NO:62. The amino acid sequences of LSR variants SEQ ID NOs:11, 13, 15, 16, 17 and 18 are shown in FIGS. 1E, 1F, 1G, 1H, 1I, and 1J, respectively. The amino acid sequence alignment of the LSR variants SEQ ID NOs: 11, 13, 15, 16, 17 and 18 with previously known LSR sequences (SEQ ID NOs: 62-67) is demonstrated in FIGS. 2B, 2C, 2D, 2E, 2F, 2G, respectively.

According to at least some embodiments, there is provided an isolated polypeptide comprising at least 98 amino acids of the soluble ectodomain of a sequence selected from the group consisting of SEQ ID NOs:11, 13, 15-18, 67, and 143; at least

62 amino acids of the soluble ectodomain of a sequence selected from the group consisting of SEQ ID NOs:1 and 58; at least 36 amino acids of the soluble ectodomain of a sequence selected from the group consisting of SEQ ID NOs:3 and 5; or at least 46 amino acids of the soluble ectodomain of SEQ ID NO:7, or an isolated polypeptide consisting essentially of an amino acid sequence as set forth in SEQ ID NO:5 or variant thereof that possesses at least 95% sequence identity therewith; or variants, or orthologs, or fragments thereof.

Optionally the isolated polypeptide comprises only between 98 to 180 amino acids of the sequence selected from the group consisting of SEQ ID NOs:11, 13, 15-18, 67, and 143; between 62 to 228 amino acids of the sequence selected from the group consisting of SEQ ID NOs:1 and 58; between 36 and 393 of the sequence selected from the group consisting of SEQ ID NOs:3 and 5; or between 46 and 216 amino acids of SEQ ID NO:7.

Also optionally, the isolated polypeptide is selected from the group consisting of a polypeptide comprising only between 98 to 118, 135 to 155, and 160 to 180 amino acids of the sequence selected from the group consisting of SEQ ID NOs:11, 13, 15-18, 67, and 143; between 62 to 82, 95 to 115, 208 to 228 amino acids of the sequence selected from the group consisting of SEQ ID NOs:1 and 58; between 36 to 70, 80 to 100, 170 to 200, 265 to 290, 365 to 393 amino acids of the sequence selected from the group consisting of SEQ ID NOs:3 and 5; or between 46 to 66, 84 to 104, 196 to 216 amino acids of SEQ ID NO:7.

Also optionally, the isolated polypeptide comprises only about 72, 106, or 218 amino acids of the sequence selected from the group consisting of SEQ ID NOs:1 and 58; about 108, 145, or 170 amino acids of the sequence selected from the group consisting of SEQ ID NOs:11, 13, 15-18, 67, and 143; about 56, 94, or 206 amino acids of SEQ ID NO:7; or about 46, 49, 58, 60, 87, 89, 93, 94, 178, 182, 185, 187, 273, 279, 282, 374 or 383 amino acids of SEQ ID NOs:3 and 5.

Also optionally, the isolated polypeptide consists essentially of an amino acid sequence having at least 95% sequence identity with amino acid sequences set forth in any one of SEQ ID NOs: 12, 2, 4-6, 8, 14, 47-50, 10, 15-18, 22, 39, 59-61; 81-102. Optionally and preferably, the isolated polypeptide consists essentially of the amino acid sequence set forth in any one of SEQ ID NOs: 12, 2, 4-6, 8, 14, 47-50, 10, 15-18, 22, 39, 59-61; 81-102.

Optionally, the isolated polypeptide blocks or inhibits the interaction of LSR, TMEM25, VSIG10, LY6G6F, or a fragment or variant thereof with a corresponding functional counterpart.

Optionally, the isolated polypeptide replaces or augments the interaction of LSR, TMEM25, VSIG10, LY6G6F, or a fragment or variant thereof with a corresponding functional counterpart.

Optionally, the isolated ortholog is a mouse polypeptide selected from SEQ ID NOs: 9 and 19-21.

According to at least some embodiments, the present invention provides isolated polypeptides comprising discrete portions (fragments) of VSIG10 proteins, corresponding to:

A. An isolated chimeric polypeptide, comprising a first amino acid sequence being at least 95% homologous to MAAGGSAPEPRVLVCLGALLAG-VWAVGLEAVVIGEVHENVTLHCGNISGLRGQ VTWYRNNSPEPVFLSSNSSLRPAEPRFSLV-DATSLHIESLSLGDEGIYTCQEILNVT QWFQVWLQVA corresponding to amino acids 1-120 of known VSIG10 protein (SEQ ID NO:3), which also corresponds to amino acids 1-120 of VSIG10 variant (SEQ ID NO:5), a second bridging

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amino acid sequence comprising of N, and a third amino acid sequence being at least 95% homologous to PPP-SAPQCWAQMASGSFMLQLTCRWDGGYPD-PDFLWIEEPGGVIVGKSKLGVE MLSESQLS-DGKKFKCVTSHIVGPESGASCMVQIRGPSLLSEPMK-TCFTGGNVTLT CQVSGAYPPAKILWLRNLTQPEVI-IQPSSRHLITQDQGQNSTLTIHNCSQDLDEGYI CRAD-SPVGVREMEIWLVSKEPLNIGGIVG-TIVSLLLLGLAIISGLLLHYSPVFCWK VGNTSRGQNMDDMVLVD-SEEEEEEEEEEEEDAAGEQEGAREREELPKEIPKQ DHIHRVTALVNGNIEQMGNFQDLQDDS-SEEQSDIVQEEEDRPV corresponding to amino acids 223-540 of known VSIG10 protein (SEQ ID NO:3), which also corresponds to amino acids 122-439 of VSIG10 variant (SEQ ID NO:5), wherein said first amino acid sequence, second bridging amino acid sequence and third amino acid sequence are contiguous and in a sequential order.

B. An isolated polypeptide of an edge portion of VSIG10 variant (SEQ ID NO:5), comprising a polypeptide having a length "n", wherein n is at least about 10 amino acids in length, optionally at least about 20 amino acids in length, preferably at least about 30 amino acids in length, more preferably at least about 40 amino acids in length and most preferably at least about 50 amino acids in length, wherein at least 3 amino acids comprise ANP having a structure as follows (numbering according to VSIG10 variant (SEQ ID NO:5)): a sequence starting from any of amino acid numbers 120-x to 120; and ending at any of amino acid numbers 122+((n-3)-x), in which x varies from 0 to n-3.

According to at least some embodiments, the subject invention further provides isolated polypeptides comprising a sequence of amino acid residues corresponding to discrete portions of VSIG10 proteins, corresponding to the new junction and edge portions of VSIG10 variant (SEQ ID NO: 5). The unique sequence of the new junction of VSIG10 variant (SEQ ID NO: 5) is demonstrated in protein sequence alignment in FIG. 2A.

According to at least some embodiments, the subject invention provides isolated polypeptides comprising discrete portions (fragments) of LSR proteins, corresponding to:

A. An isolated chimeric polypeptide, comprising a first amino acid sequence being at least 95% homologous to MALLAGLSRGLGSHPAAGRAV-VFVWLLSTWCTAPARAIQVTVSNPYHV-ILFQPVTLPCYQMTSTPTQPIVI-WKYKSFCDRIADAFSPASVDNQLNAQLAAGN PGY-NPYVECQDSVRTVRVATKQG-NAVTLGDYQYQGRITITGNADLTEDQTAW GDSGVYYCSVVSAQDLQGNNEAYAEILV-LGRTSGVAELLPGFQAGPIE corresponding to amino acids 49-258 of known LSR protein (SEQ ID NO:62), which also corresponds to amino acids 1-210 of LSR variant isoform f (SEQ ID NO:18), a second bridging amino acid sequence comprising of V, and a third amino acid sequence being at least 95% homologous to YAAGKAATSGVPSIYAP-STYHLSPAKTPPPAMIPMGPAYN-GYPGGYPGDVDRS SSAGGQGSYVPLLRDTS-VASEVRSGYRIQASQDDSMRVLYYMEKELANFDP SRPGPPSGRVERAMSEVTSLED-DWRSRPSRGPALTPIRDEEWGGHSPRSPRGWD QEPAREQAGGWRARRPRARSVDALD-DLTPSTAESGSRPTSNGGRSRAYMPP RSRSRDDLY-DQDDSRDFPRSRDPHYDDFRSRERPPAD-PRSHHHRTDPRDNGSRSGDLPYDGRLLLEAVRKKGSEERRRPH-KEEEEEAYYPPAPPYSETDSQASRRRL KKNLA-

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LSRESLVV corresponding to amino acids 309-649 of known LSR protein (SEQ ID NO:62), which also corresponds to amino acids 212-552 of LSR variant isoform f (SEQ ID NO:18), wherein said first amino acid sequence, second bridging amino acid and third amino acid sequence are contiguous and in a sequential order.

B. An isolated polypeptide of an edge portion of LSR variant isoform f (SEQ ID NO:18), comprising a polypeptide having a length "n", wherein n is at least about 10 amino acids in length, optionally at least about 20 amino acids in length, preferably at least about 30 amino acids in length, more preferably at least about 40 amino acids in length and most preferably at least about 50 amino acids in length, wherein at least 3 amino acids comprise EVY having a structure as follows (numbering according to SEQ ID NO:18): a sequence starting from any of amino acid numbers 210-x to 210; and ending at any of amino acid numbers 212+((n-3)-x), in which x varies from 0 to n-3.

C. An isolated chimeric polypeptide comprising a first amino acid sequence being at least 95% homologous to MALLAGLSRGLGSHPAAGRAV-VFVWLLSTWCTAPARAIQVTVSNPYHV-ILFQPVTLPCYQMTSTPTQPIVI-WKYKSFCDRIADAFSPASVDNQLNAQLAAGN PGY-NPYVECQDSVRTVRVATKQG-NAVTLGDYQYQGRITITGNADLTEDQTAW GDSGVYYCSVVSAQDLQGNNEAYAEILV corresponding to amino acids 49-239 of known LSR protein (SEQ ID NO:66), which also corresponds to amino acids 1-191 of LSR variant isoform f (SEQ ID NO:18), a second amino acid sequence being at least 80%, preferably at least 85%, more preferably at least 90% and most preferably at least 95% homologous to a polypeptide having the sequence GRTSG-VAELLPGFQAGPIE corresponding to amino acids 192-218 of LSR variant isoform f (SEQ ID NO:18), and a third amino acid sequence being at least 95% homologous to VYAAGKAATSGVPSIYAPSTYHLSPAKTPPP-PAMIPMGPAYNGYPGGYPGDVD RSSAGGQGSYV-PLLRDTSVASEVRSGYRIQASQDDSMRVLYYMEKELANF DPSRPGPPSGRVERAMSEVTSLED-DWRSRPSRGPALTPIRDEEWGGHSPRSPRG WDQE-PAREQAGGWRARRPRARSVDALD-DLTPSTAESGSRPTSNGGRSRAYMPPRSRSDLYDQDDSRDFPRSRDPHY-DDFRSRERPPADPRSHHHRTDPRDNGSRSGDLPYDGRLLLEAVRKKGSEERRRPH-KEEEEEAYYPPAPPYSETDSQASR ERRLKKNLALSRESLVV corresponding to amino acids 240-581 of known LSR protein SEQ ID NO:66, which also corresponds to amino acids 211-552 of LSR variant isoform f (SEQ ID NO:18), wherein said first amino acid sequence, second amino acid sequence and third amino acid sequence are contiguous and in a sequential order.

D. An isolated polypeptide of an edge portion of LSR variant isoform f (SEQ ID NO:18), comprising an amino acid sequence being at least about 80%, preferably at least about 85%, more preferably at least about 90% and most preferably at least about 95% homologous to the sequence GRTSG-VAELLPGFQAGPIE of LSR variant isoform f (SEQ ID NO:18).

According to at least some embodiments, the subject invention further provides isolated polypeptides comprising a sequence of amino acid residues corresponding to discrete portions of LSR, corresponding to the new junction and edge portions of LSR variant LSR isoform-f (SEQ ID NO: 18). The

unique sequences of the new junction of the LSR isoform-f (SEQ ID NO: 18) is demonstrated in protein sequence alignment in FIG. 2G.

According to at least some embodiments, the subject invention provides polypeptides comprising a sequence of amino acid residues corresponding to discrete portions of LY6G6F, VSIG10, TMEM25 and/or LSR proteins, including different portions of the extracellular domain corresponding to residues 17-234 of LY6G6F (SEQ ID NO:1), corresponding to amino acid sequence depicted in SEQ ID NO:2; residues 31-413 of VSIG10 (SEQ ID NO:3), corresponding to amino acid sequence depicted in SEQ ID NO:4; residues 31-312 of VSIG10 (SEQ ID NO:5), corresponding to amino acid sequence depicted in SEQ ID NO:6; residues 27-232 of TMEM25 (SEQ ID NO:7), corresponding to amino acid sequence depicted in SEQ ID NO:8; residues 42-211 of LSR (SEQ ID NO:11, and/or SEQ ID NO:143), corresponding to amino acid sequence depicted in SEQ ID NO:12; residues 42-192 of LSR (SEQ ID NO:13), corresponding to amino acid sequence depicted in SEQ ID NO:14, residues 42-533 of LSR (SEQ ID NO:15), corresponding to amino acid sequence depicted in SEQ ID NO:47, residues 42-532 of LSR (SEQ ID NO:16), corresponding to amino acid sequence depicted in SEQ ID NO:48, residues 42-493 of LSR (SEQ ID NO:17), corresponding to amino acid sequence depicted in SEQ ID NO:49, residues 42-552 of LSR (SEQ ID NO:18), corresponding to amino acid sequence depicted in SEQ ID NO:50, and/or fragments and/or variants thereof possessing at least 85%, 90%, 95, 96, 97, 98 or 99% sequence homology therewith. According to still further embodiments, the LY6G6F ECD fragments are selected from any one of SEQ ID NOs 81, 96, and variants thereof, as described herein. According to still further embodiments, the VSIG10 ECD fragments are selected from any one of SEQ ID NOs 82-93, 97-100, and variants thereof, as described herein. According to still further embodiments, the LSR ECD fragments are selected from any one of SEQ ID NOs 95, 102, and variants thereof, as described herein. According to still further embodiments, the TMEM25 ECD fragments are selected from any one of SEQ ID NOs 94, 101, and variants thereof, as described herein. According to still further embodiments, the discrete portions of LY6G6F, VSIG10, TMEM25 and/or LSR proteins may or may not include a signal (leader) peptide (SP) sequence (FIG. 1). According to at least some embodiments of the invention, there are provided examples of the ECD portions including SP sequences of LY6G6F, VSIG10, TMEM25 and/or LSR proteins. An example of ECD portion including SP sequence of LY6G6F protein (SEQ ID NO:1) is amino acid sequence set forth in SEQ ID NO:59. An example of ECD portion including SP sequence of VSIG10 protein (SEQ ID NO:3) is amino acid sequence set forth in SEQ ID NO:60. An example of ECD portion including SP sequence of VSIG10 protein (SEQ ID NO:5) is amino acid sequence set forth in SEQ ID NO:61. An example of ECD portion including SP sequence of TMEM25 protein (SEQ ID NO:7) is amino acid sequence set forth in SEQ ID NO: 39. An example of ECD portion including SP sequence of LSR protein (SEQ ID NO:11) is amino acid sequence set forth in SEQ ID NO:10. An example of ECD portion including SP sequence of LSR protein (SEQ ID NO:14) is amino acid sequence set forth in SEQ ID NO:22.

According to further embodiments, the invention provides polypeptides comprising a sequence of amino acid residues corresponding to soluble LSR proteins depicted in SEQ ID NO: 18, including different portions thereof or variants thereof possessing at least 85%, 90%, 95, 96, 97, 98 or 99% sequence homology therewith. According to further embodiments, the invention provides polypeptides comprising a

sequence of amino acid residues corresponding to soluble LSR proteins depicted in any one of SEQ ID NOs:15-16, including different portions thereof or variants thereof possessing at least 95, 96, 97, 98 or 99% sequence homology therewith. According to further embodiments, the invention provides polypeptides comprising a sequence of amino acid residues corresponding to soluble LSR proteins depicted in any one of SEQ ID NOs:15-18. According to still further embodiments, the soluble LSR proteins depicted in any one of SEQ ID NOs:15-18 may or may not include a signal (leader) peptide sequence (FIGS. 1G, G, I and J).

According to still further embodiments, the invention provides polypeptides comprising a sequence of amino acid residues corresponding to extracellular domains of orthologs of TMEM25, LY6G6F, VSIG10, LSR variant 1 and/or LSR variant 2 proteins, particularly mouse orthologs (SEQ ID NOs: 28, 29, 30, 31 and/or 32, respectively), including but not limited to mouse orthologs extracellular domains corresponding to amino acid sequence depicted in SEQ ID NOs: 9, 19-21, or portions or variants thereof possessing at least 85%, 90%, 95, 96, 97, 98 or 99% sequence homology therewith.

According to still further embodiments, the invention provides polypeptides comprising an amino acid sequence corresponding to any one of novel variants of VSIG10 (SEQ ID NO: 5), and LSR (SEQ ID NOs: 11, 13, 15, 16 and 18).

According to at least some embodiments, the present invention provides a fusion protein comprising any of the above polypeptides joined to a heterologous sequence. Optionally, the heterologous sequence comprises at least a portion of an immunoglobulin molecule. Optionally and preferably, the immunoglobulin molecule portion is an immunoglobulin heavy chain constant region Fc fragment. Optionally and more preferably, the immunoglobulin heavy chain constant region is derived from an immunoglobulin isotype selected from the group consisting of an IgG1, IgG2, IgG3, IgG4, IgM, IgE, IgA and IgD. Optionally and most preferably, the fusion protein has the amino acid sequence set forth in any one of SEQ ID NOs: 71-80, 172-181 or set forth in any one of SEQ ID NOs:23-26 and also optionally modulates immune cell response in vitro or in vivo.

According to at least some embodiments, the subject invention provides isolated nucleic acid sequences encoding any one of the foregoing novel variants of TMEM25, VSIG10, and/or LSR and/or any one of the foregoing LY6G6F, VSIG10, TMEM25 and/or LSR extracellular domain polypeptides or fragments or homologs or orthologs thereof.

According to at least some embodiments, there is provided an isolated nucleic acid sequence selected from the group consisting of SEQ ID NOs: 33-37, 40-46, 132, 155, 182-198, or variant thereof that possesses at least 95% sequence identity therewith, or a degenerative variant thereof.

According to at least some embodiments, the subject invention provides an isolated polynucleotide encoding a polypeptide comprising any one of the amino acid sequences, as set forth in SEQ ID NOs: 2, 4, 5, 6, 8-16, 18-22, 39, 47-50, 59-61, 143, or a fragment or variant thereof that possesses at least 85, 90, 95, 96, 97, 98 or 99% sequence identity therewith, or a degenerative variant thereof.

According to at least some embodiments, the subject invention provides an isolated polynucleotide comprising a nucleic acid as set forth in any one of SEQ ID NO:33-37, 40-46, 132, 145, 155, 182-188, or a sequence homologous thereto or degenerative variants thereof. According to another embodiment, the isolated polynucleotide is at least 85, 90, 95, 96, 97, 98 or 99% homologous to a nucleic acid sequence as set forth in any one of SEQ ID NOs: 33-37, 40-46, 145.

According to at least some embodiments, there is provided an expression vector or a virus, containing at least one isolated nucleic acid sequence as described herein. According to at least some embodiments, there is provided a recombinant cell comprising an expression vector or a virus containing an isolated nucleic acid sequence as described herein, wherein the cell constitutively or inducibly expresses the polypeptide encoded by the DNA segment. According to at least some embodiments, there is provided a method of producing a LSR, TMEM25, VSIG10, LY6G6F soluble ectodomain polypeptide, or fragment or fusion protein thereof, comprising culturing the recombinant cell as described herein, under conditions whereby the cell expresses the polypeptide encoded by the DNA segment or nucleic acid and recovering said polypeptide.

According to at least some embodiments of the present invention, there is provided a pharmaceutical composition comprising an isolated amino acid sequence of ectodomain or soluble or secreted forms of any one of LY6G6F, VSIG10, TMEM25, LSR proteins or variants or orthologs or fragments or conjugates containing same.

According to at least some embodiments, the invention provides an isolated or purified amino acid sequence of soluble and/or extracellular domain of LY6G6F, VSIG10, TMEM25 and/or LSR protein or nucleic acid sequence encoding same, which optionally may be directly or indirectly attached to a non-LY6G6F, VSIG10, TMEM25 and/or LSR protein or nucleic acid sequence, such as a soluble immunoglobulin domain or fragment.

According to at least some embodiments, the invention provides vectors such as plasmids and recombinant viral vectors and host cells containing that express secreted or soluble form and/or the ECD of the LY6G6F, VSIG10, TMEM25 and/or LSR protein or fragments or variants or orthologs thereof or polypeptide conjugates containing any of the foregoing.

According to at least some embodiments the invention provides a use of these vectors such as plasmids and recombinant viral vectors and host cells containing that express any one of LY6G6F, VSIG10, TMEM25 and/or LSR, secreted and/or soluble form and/or the ECD and/or fragments thereof and/or variants, and/or orthologs thereof and/or polypeptide conjugates containing any of the foregoing to produce any one of said LY6G6F, VSIG10, TMEM25 and/or LSR proteins.

According to at least some embodiments, the invention provides pharmaceutical or diagnostic compositions containing any of the foregoing.

According to at least some embodiments, the invention provides a use of any one of the compounds containing at least one of LY6G6F, VSIG10, TMEM25 and/or LSR ectodomains, soluble or secreted form or fragments or orthologs or variants thereof, or conjugates, or nucleic acid sequence encoding same, or pharmaceutical composition comprising same, as therapeutics for treatment or prevention of cancer as recited herein, infectious disorder as recited herein, and/or immune related disorder, including but not limited to autoimmune diseases as recited herein, transplant rejection and graft versus host disease and/or for blocking or promoting immune costimulation mediated by any one of the LY6G6F, VSIG10, TMEM25 and/or LSR polypeptides, immune related diseases as recited herein and/or for immunotherapy (promoting or inhibiting immune costimulation). According to at least some embodiments, the autoimmune disease includes any autoimmune disease, and optionally and preferably includes but is not limited to any of the types and subtypes of any of multiple sclerosis, rheumatoid arthritis,

type I diabetes, psoriasis, systemic lupus erythematosus, inflammatory bowel disease, uveitis, or Sjogren's syndrome.

According to at least some embodiments, the invention provides a use of any one of the compounds containing at least one of LY6G6F, VSIG10, TMEM25 and/or LSR ectodomains, soluble or secreted form or fragments or orthologs or variants thereof, or conjugates, or nucleic acid sequence encoding same, or pharmaceutical composition comprising same, for administration as an anti-cancer vaccine, as an adjuvant for anti cancer vaccine, and/or for adoptive immunotherapy, and/or for immunotherapy of cancer as recited herein.

According to at least some embodiments, the invention provides a use of any of the LY6G6F, VSIG10, TMEM25 and/or LSR proteins, and/or nucleic acid sequences as targets for development of drugs which specifically bind to any one of the LY6G6F, VSIG10, TMEM25 and/or LSR proteins and/or drugs which agonize or antagonize the binding of other moieties to the LY6G6F, VSIG10, TMEM25 and/or LSR proteins.

According to at least some embodiments, the present invention provides drugs which modulate (agonize or antagonize) at least one of the LY6G6F, VSIG10, TMEM25 and/or LSR related biological activity. Such drugs include by way of example antibodies, small molecules, peptides, ribozymes, aptamers, antisense molecules, siRNA's and the like. These molecules may directly bind or modulate an activity elicited by the any one of the LY6G6F, VSIG10, TMEM25 and/or LSR proteins or the LY6G6F, VSIG10, TMEM25 and/or LSR DNA or portions or variants thereof or may indirectly modulate any one of the LY6G6F, VSIG10, TMEM25 and/or LSR associated activity or binding of molecules to any one of the LY6G6F, VSIG10, TMEM25 and/or LSR and portions and variants thereof such as by modulating the binding of any one of LY6G6F, VSIG10, TMEM25 and/or LSR to its counter-receptor or endogenous ligand.

According to at least some embodiments, the invention provides novel monoclonal or polyclonal antibodies and antigen binding fragments and conjugates containing same, and/or alternative scaffolds, that specifically bind any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins as described herein or polypeptides having at least 95% homology thereto. Optionally such antibodies bind to proteins selected from the group consisting of any one of SEQ ID NOs: 1-8, 10-18, 22, 39, 47-50, 59-61, 9, 19-21, and/or the amino acid sequences corresponding to the unique edges of any one of SEQ ID NOs: 5 and 18, particularly wherein these antibodies, antigen binding fragments and conjugates containing same, and/or alternative scaffolds, are adapted to be used as therapeutic and/or diagnostic agents (both in vitro and in vivo diagnostic methods), particularly for treatment and/or diagnosis of infectious disorder as recited herein, and/or immune related disorder, including but not limited to autoimmune diseases as recited herein, immune related diseases as recited herein, transplant rejection and graft versus host disease, as well as cancers and malignancies as recited herein.

According to at least some embodiments, there are provided antibodies in which the antigen binding site comprises a conformational or linear epitope, and wherein the antigen binding site contains about 3-7 contiguous or non-contiguous amino acids. Optionally, the antibody is a fully human antibody, chimeric antibody, humanized or primatized antibody.

Also optionally, the antibody is selected from the group consisting of Fab, Fab', F(ab')₂, F(ab)', F(ab), Fv or scFv fragment and minimal recognition unit.

Also optionally, the antibody is coupled to a moiety selected from a drug, a radionuclide, a fluorophore, an

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enzyme, a toxin, a therapeutic agent, or a chemotherapeutic agent; and wherein the detectable marker is a radioisotope, a metal chelator, an enzyme, a fluorescent compound, a bioluminescent compound or a chemiluminescent compound.

Also optionally the antibody blocks or inhibits the interaction of any one of LSR, TMEM25, VSIG10, LY6G6F polypeptides, or a fragment or variant thereof with a counterpart.

Also optionally the antibody replaces or augments the interaction of LSR, TMEM25, VSIG10, LY6G6F polypeptides, or a fragment or variant thereof with a counterpart.

Also optionally the antibody elicits apoptosis or lysis of cancer cells that express any one of LSR, TMEM25, VSIG10, LY6G6F protein.

Also optionally the apoptosis or lysis involves CDC or ADCC activity of the antibody, wherein CDC (complement dependent cytotoxicity) or ADCC (antibody dependent cellular cytotoxicity) activities are used to target the immune cells.

According to at least some embodiments, the invention provides antibodies and antigen binding fragments and conjugates containing same, and/or alternative scaffolds, against discrete portions of the LY6G6F protein including different portions of the extracellular domain corresponding to residues 17-234 of LY6G6F (SEQ ID NO:1), set forth in SEQ ID NO: 2, and/or corresponding to amino acid sequences set forth in any one of SEQ ID NOs: 81, 96. According to further embodiments the invention provides antibodies antigen binding fragments and conjugates containing same, and/or alternative scaffolds, against discrete portions of the mouse LY6G6F protein (SEQ ID NO: 29), including different portions of the extracellular domain corresponding to SEQ ID NO:20.

According to at least some embodiments, the invention provides antibodies and antigen binding fragments and conjugates containing same, and/or alternative scaffolds, against discrete portions of the VSIG10 protein including different portions of the extracellular domain corresponding to amino acid residues 31-413 of VSIG10 (SEQ ID NO:3), depicted in SEQ ID NO:4; amino acid residues 31-312 of VSIG10 (SEQ ID NO:5), depicted in SEQ ID NO:6, and/or corresponding to amino acid sequences set forth in any one of SEQ ID NOs: 82-93, 97-100. According to further embodiments the invention provides antibodies antigen binding fragments and conjugates containing same, and/or alternative scaffolds, against discrete portions of the mouse VSIG10 protein (SEQ ID NO: 30), including different portions of the extracellular domain corresponding to SEQ ID NO:19. According to at least some embodiments, the invention provides antibodies, antigen binding fragments and conjugates containing same, and/or alternative scaffolds, against discrete portions of the VSIG10 protein including the edge portion of VSIG10 variant (SEQ ID NO:5), as described herein.

According to at least some embodiments, the invention provides antibodies, antigen binding fragments and conjugates containing same, and/or alternative scaffolds, against discrete portions of the TMEM25 proteins including different portions of the extracellular domain corresponding to amino acid residues 27-232 of TMEM25 (SEQ ID NO:7), depicted in SEQ ID NO:8, and/or corresponding to amino acid sequences set forth in any one of SEQ ID NOs: 94, 101. According to further embodiments the invention provides antibodies and antigen binding fragments and conjugates containing same, and/or alternative scaffolds, against discrete portions of the mouse TMEM25 protein (SEQ ID NO: 28), including different portions of the extracellular domain, set forth in SEQ ID NO:9.

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According to at least some embodiments, the invention provides antibodies and antigen binding fragments and conjugates containing same, and/or alternative scaffolds, against discrete portions of the LSR proteins including different portions of the extracellular domain corresponding to amino acid residues 42-211 of LSR (SEQ ID NO:11), depicted in SEQ ID NO:12; amino acid residues 42-192 of LSR (SEQ ID NO:13), depicted in SEQ ID NO:14, amino acid residues 42-533 of LSR (SEQ ID NO:15), depicted in SEQ ID NO:47, amino acid residues 42-532 of LSR (SEQ ID NO:16), depicted in SEQ ID NO:48, amino acid residues 42-493 of LSR (SEQ ID NO:17), depicted in SEQ ID NO:49, amino acid residues 42-552 of LSR (SEQ ID NO:18), depicted in SEQ ID NO:50, and/or corresponding to amino acid sequences set forth in any one of SEQ ID NOs:95, 102. According to further embodiments the invention provides antibodies and antigen binding fragments and conjugates containing same, and/or alternative scaffolds, against discrete portions of the mouse LY6G6F proteins (SEQ ID NOs: 31-32), including different portions of the extracellular domain corresponding to SEQ ID NO:21.

According to at least some embodiments, the invention provides antibodies and antigen binding fragments and conjugates containing same, and/or alternative scaffolds, against discrete portions of the LSR proteins including the unique edge portion of LSR variant isoform-f (SEQ ID NO:18), as described herein.

According to at least some embodiments, the invention provides antibodies and antigen binding fragments and conjugates containing same, and/or alternative scaffolds, against discrete portions of the soluble LSR proteins including different portions of the LSR proteins depicted in any one of SEQ ID NOs:15-18, 47-50.

According to at least some embodiments the invention relates to protein scaffolds with specificities and affinities in a range similar to specific antibodies. According to at least some embodiments the present invention relates to an antigen-binding construct comprising a protein scaffold which is linked to one or more epitope-binding domains. Such engineered protein scaffolds are usually obtained by designing a random library with mutagenesis focused at a loop region or at an otherwise permissible surface area and by selection of variants against a given target via phage display or related techniques. According to at least some embodiments the invention relates to alternative scaffolds including, but not limited to, anticalins, DARPin, Armadillo repeat proteins, protein A, lipocalins, fibronectin domain, ankyrin consensus repeat domain, thioredoxin, chemically constrained peptides and the like. According to at least some embodiments the invention relates to alternative scaffolds that are used as therapeutic agents for treatment of cancer as recited herein, immune related diseases as recited herein, autoimmune disease as recited herein and infectious diseases, as well as for in vivo diagnostics.

According to at least some embodiments of the present invention, there is provided a pharmaceutical composition comprising an isolated polypeptide as described herein, or a fusion protein as described herein; a nucleotide sequence as described herein; an expression vector as described herein; a host cell as described herein, or an antibody as described herein, and further comprising a pharmaceutically acceptable diluent or carrier.

According to at least some embodiments, there is provided use of any of any one of an isolated polypeptide as described herein, or a fusion protein as described herein; a nucleotide sequence as described herein; an expression vector as described herein; a host cell as described herein, or an antibody as described herein or a pharmaceutical composition as

described herein, wherein administration of such to the subject inhibits or reduces activation of T cells.

According to at least some embodiments, there is provided use of any of any one of an isolated polypeptide as described herein, or a fusion protein as described herein; a nucleotide sequence as described herein; an expression vector as described herein; a host cell as described herein, or an antibody as described herein or a pharmaceutical composition as described herein, for treatment of cancer.

According to at least some embodiments, there is provided use of an isolated polypeptide as described herein, or a fusion protein as described herein; a nucleotide sequence as described herein; an expression vector as described herein; a host cell as described herein, or an antibody as described herein or a pharmaceutical composition as described herein, for treatment of infectious disorder.

According to at least some embodiments, there is provided a method of performing one or more of the following in a subject:

- a. upregulating cytokines;
- b. inducing expansion of T cells;
- c. promoting antigenic specific T cell immunity;
- d. promoting CD4+ and/or CD8+ T cell activation;

comprising administering any of an isolated polypeptide as described herein, or a fusion protein as described herein; a nucleotide sequence as described herein; an expression vector as described herein; a host cell as described herein, or an antibody as described herein or a pharmaceutical composition as described herein to the subject.

According to at least some embodiments, there is provided a method for treating or preventing immune system related condition comprising administering to a subject in need thereof an effective amount of any of an isolated polypeptide as described herein, or a fusion protein as described herein; a nucleotide sequence as described herein; an expression vector as described herein; a host cell as described herein, or an antibody as described herein or a pharmaceutical composition.

Optionally, the immune system related condition comprises an immune related condition, autoimmune diseases as recited herein, transplant rejection and graft versus host disease and/or for blocking or promoting immune costimulation mediated by any one of the LSR, TMEM25, VSIG10, and/or LY6G6F polypeptides, immune related diseases as recited herein and/or for immunotherapy (promoting or inhibiting immune costimulation).

Optionally the treatment is combined with another moiety useful for treating immune related condition.

Optionally the moiety is selected from the group consisting of immunosuppressants such as corticosteroids, cyclosporin, cyclophosphamide, prednisone, azathioprine, methotrexate, rapamycin, tacrolimus, biological agents such as TNF-alpha blockers or antagonists, or any other biological agent targeting any inflammatory cytokine, nonsteroidal antiinflammatory drugs/Cox-2 inhibitors, hydroxychloroquine, sulphasalazopyrine, gold salts, etanercept, infliximab, mycophenolate mofetil, basiliximab, atacicept, rituximab, cytoxin, interferon beta-1a, interferon beta-1b, glatiramer acetate, mitoxantrone hydrochloride, anakinra and/or other biologics and/or intravenous immunoglobulin (IVIG), interferons such as IFN-beta-1a (REBIF® and AVONEX®) and IFN-beta-1b (BETASERON®); glatiramer acetate (COPAX-ONE®), a polypeptide; natalizumab (TYSABRI®), mitoxantrone (NOVANTRONE®), a cytotoxic agent, a calcineurin inhibitor, e.g. cyclosporin A or FK506; an immunosuppressive macrolide, e.g. rapamycin or a derivative thereof; e.g. 40-O-(2-hydroxy)ethyl-rapamycin, a lymphocyte homing

agent, e.g. FTY720 or an analog thereof, corticosteroids; cyclophosphamide; azathioprine; methotrexate; leflunomide or an analog thereof; mizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualine or an analog thereof; immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD 11a/CD18, CD7, CD25, CD 27, B7, CD40, CD45, CD58, CD 137, ICOS, CD150 (SLAM), OX40, 4-1BB or their ligands; or other immunomodulatory compounds, e.g. CTLA4-Ig (abatacept, ORENCIA®), CD28-Ig, B7-H4-Ig, or other costimulatory agents, or adhesion molecule inhibitors, e.g. mAbs or low molecular weight inhibitors including LFA-1 antagonists, Selectin antagonists and VLA-4 antagonists, or another immunomodulatory agent.

Optionally the immune condition is selected from autoimmune disease, transplant rejection, or graft versus host disease.

Optionally the autoimmune disease is selected from a group consisting of multiple sclerosis, including relapsing-remitting multiple sclerosis, primary progressive multiple sclerosis, and secondary progressive multiple sclerosis; psoriasis; rheumatoid arthritis; psoriatic arthritis, systemic lupus erythematosus (SLE); ulcerative colitis; Crohn's disease; benign lymphocytic angiitis, thrombocytopenic purpura, idiopathic thrombocytopenia, idiopathic autoimmune hemolytic anemia, pure red cell aplasia, Sjogren's syndrome, rheumatic disease, connective tissue disease, inflammatory rheumatism, degenerative rheumatism, extra-articular rheumatism, juvenile rheumatoid arthritis, arthritis uratica, muscular rheumatism, chronic polyarthritis, cryoglobulinemic vasculitis, ANCA-associated vasculitis, antiphospholipid syndrome, myasthenia gravis, autoimmune haemolytic anaemia, Guillian-Barre syndrome, chronic immune polyneuropathy, autoimmune thyroiditis, insulin dependent diabetes mellitus, type I diabetes, Addison's disease, membranous glomerulonephropathy, Goodpasture's disease, autoimmune gastritis, autoimmune atrophic gastritis, pernicious anaemia, pemphigus, pemphigus vulgaris, cirrhosis, primary biliary cirrhosis, dermatomyositis, polymyositis, fibromyositis, myogelosis, celiac disease, immunoglobulin A nephropathy, Henoch-Schonlein purpura, Evans syndrome, atopic dermatitis, psoriasis, psoriasis arthropathica, Graves' disease, Graves' ophthalmopathy, scleroderma, systemic scleroderma, progressive systemic scleroderma, asthma, allergy, primary biliary cirrhosis, Hashimoto's thyroiditis, primary myxedema, sympathetic ophthalmia, autoimmune uveitis, hepatitis, chronic action hepatitis, collagen diseases, ankylosing spondylitis, periartthritis humeroscapularis, panarteritis nodosa, chondrocalcinosis, Wegener's granulomatosis, microscopic polyangiitis, chronic urticaria, bullous skin disorders, pemphigoid, atopic eczema, Devic's disease, childhood autoimmune hemolytic anemia, Refractory or chronic Autoimmune Cytopenias, Prevention of development of Autoimmune Anti-Factor VIII Antibodies in Acquired Hemophilia A, Cold Agglutinin Disease, Neuromyelitis Optica, Stiff Person Syndrome, gingivitis, periodontitis, pancreatitis, myocarditis, vasculitis, gastritis, gout, gouty arthritis, and inflammatory skin disorders, selected from the group consisting of psoriasis, atopic dermatitis, eczema, rosacea, urticaria, and acne, normocomplementemic urticarial vasculitis, pericarditis, myositis, anti-synthetase syndrome, scleritis, macrophage activation syndrome, Bechet's Syndrome, PAPA Syndrome, Blau's Syndrome, gout, adult and juvenile Still's disease, cryopyrinopathy, Muckle-Wells syndrome, familial cold-induced auto-inflammatory syndrome, neonatal onset multisystemic inflammatory disease, familial Mediterranean fever, chronic infantile neurologic, cutaneous and

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articular syndrome, systemic juvenile idiopathic arthritis, Hyper IgD syndrome, Schnitzler's syndrome, autoimmune retinopathy, age-related macular degeneration, atherosclerosis, chronic prostatitis and TNF receptor-associated periodic syndrome (TRAPS).

Optionally the autoimmune disease is selected from the group consisting of any of the types and subtypes of any of multiple sclerosis, rheumatoid arthritis, type I diabetes, psoriasis, systemic lupus erythematosus, inflammatory bowel disease, uveitis, and Sjogren's syndrome.

According to at least some embodiments there is provided a method for treating or preventing an infectious disease comprising administering to a subject in need thereof an effective amount of any of an isolated polypeptide as described herein, or a fusion protein as described herein; a nucleotide sequence as described herein; an expression vector as described herein; a host cell as described herein, or an antibody as described herein or a pharmaceutical composition.

Optionally the infectious disease is selected from the disease caused by bacterial infection, viral infection, fungal infection and/or other parasite infection.

Optionally the infectious disease is selected from hepatitis B, hepatitis C, infectious mononucleosis, EBV, cytomegalovirus, AIDS, HIV-1, HIV-2, tuberculosis, malaria and schistosomiasis.

According to at least some embodiments, there is provided a method for treating or preventing cancer comprising administering to a subject in need thereof an effective amount of any of an isolated polypeptide as described herein, or a fusion protein as described herein; a nucleotide sequence as described herein; an expression vector as described herein; a host cell as described herein, or an antibody as described herein or a pharmaceutical composition.

Optionally the treatment is combined with another moiety or therapy useful for treating cancer.

Optionally the therapy is radiation therapy, antibody therapy, chemotherapy, photodynamic therapy, adoptive T cell therapy, Treg depletion, surgery or in combination therapy with conventional drugs.

Optionally the moiety is selected from the group consisting of immunosuppressants, cytotoxic drugs, tumor vaccines, antibodies (e.g. bevacizumab, erbitux), peptides, peptibodies, small molecules, chemotherapeutic agents such as cytotoxic and cytostatic agents (e.g. paclitaxel, cisplatin, vinorelbine, docetaxel, gemcitabine, temozolomide, irinotecan, 5FU, carboplatin), immunological modifiers such as interferons and interleukins, immunostimulatory antibodies, growth hormones or other cytokines, folic acid, vitamins, minerals, aromatase inhibitors, RNAi, Histone Deacetylase Inhibitors, and proteasome inhibitors.

Optionally the cancer is selected from a group consisting of breast cancer, cervical cancer, ovary cancer, endometrial cancer, melanoma, bladder cancer, lung cancer, pancreatic cancer, colon cancer, prostate cancer, leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, B-cell lymphoma, Burkitt's lymphoma, multiple myeloma, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, myeloid leukemia, acute myelogenous leukemia (AML), chronic myelogenous leukemia, thyroid cancer, thyroid follicular cancer, myelodysplastic syndrome (MDS), fibrosarcomas and rhabdomyosarcomas, melanoma, uveal melanoma, teratocarcinoma, neuroblastoma, glioma, glioblastoma, benign tumor of the skin, keratoacanthomas, renal cancer, anaplastic large-cell lymphoma, esophageal squamous cells carcinoma, hepatocellular carcinoma, follicular dendritic cell carcinoma, intestinal cancer, muscle-invasive cancer, seminal vesicle

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tumor, epidermal carcinoma, spleen cancer, bladder cancer, head and neck cancer, stomach cancer, liver cancer, bone cancer, brain cancer, cancer of the retina, biliary cancer, small bowel cancer, salivary gland cancer, cancer of uterus, cancer of testicles, cancer of connective tissue, prostatic hypertrophy, myelodysplasia, Waldenstrom's macroglobinaemia, nasopharyngeal, neuroendocrine cancer, myelodysplastic syndrome, mesothelioma, angiosarcoma, Kaposi's sarcoma, carcinoid, oesophagogastric, fallopian tube cancer, peritoneal cancer, papillary serous mullerian cancer, malignant ascites, gastrointestinal stromal tumor (GIST), Li-Fraumeni syndrome and Von Hippel-Lindau syndrome (VHL), and wherein the cancer is non-metastatic, invasive or metastatic.

Optionally the cancer is any of melanoma, cancer of liver, renal, brain, breast, colon, lung, ovary, pancreas, prostate, stomach, multiple myeloma, Hodgkin's lymphoma, non Hodgkin's lymphoma, acute and chronic lymphoblastic leukemia and acute and chronic myeloid leukemia.

According to at least some embodiments, there is provided a method for potentiating a secondary immune response to an antigen in a patient, which method comprises administering effective amount of any of an isolated polypeptide as described herein, or a fusion protein as described herein; a nucleotide sequence as described herein; an expression vector as described herein; a host cell as described herein, or an antibody as described herein or a pharmaceutical composition.

Optionally the antigen is a cancer antigen, a viral antigen or a bacterial antigen, and the patient has received treatment with an anticancer vaccine or a viral vaccine.

A method of immunotherapy in a patient, comprising:

in vivo or ex vivo tolerance induction, comprising administering effective amount of any of an isolated polypeptide as described herein, or a fusion protein as described herein; a nucleotide sequence as described herein; an expression vector as described herein; a host cell as described herein, or an antibody as described herein or a pharmaceutical composition, to a patient or to leukocytes isolated from the patient, in order to induce differentiation of tolerogenic regulatory cells; ex-vivo enrichment and expansion of said cells; reinfusion of the tolerogenic regulatory cells to said patient.

A method of using at least one of: any of an isolated polypeptide as described herein, or a fusion protein as described herein; a nucleotide sequence as described herein; an expression vector as described herein; a host cell as described herein, or an antibody as described herein or a pharmaceutical composition; as a cancer vaccine adjuvant, comprising administration to a patient an immunogenic amount of a tumor associated antigen preparation of interest; and a cancer vaccine adjuvant in a formulation suitable for immunization, wherein the immune response against the tumor associated antigen in the presence of the cancer vaccine adjuvant is stronger than in the absence of the cancer vaccine adjuvant.

According to at least some embodiments there is provided a method for combining therapeutic vaccination with an antigen along with administration of any of an isolated polypeptide as described herein, or a fusion protein as described herein; a nucleotide sequence as described herein; an expression vector as described herein; a host cell as described herein, or an antibody as described herein or a pharmaceutical composition, for treatment of infection.

According to at least some embodiments, there is provided a method for combining any of an isolated polypeptide as described herein, or a fusion protein as described herein; a nucleotide sequence as described herein; an expression vec-

tor as described herein; a host cell as described herein, or an antibody as described herein or a pharmaceutical composition, an adjuvant, and an antigen in a vaccine, in order to increase the immune response.

Optionally the antigen is a viral antigen, bacterial antigen, fungal antigen, parasite antigen, and/or other pathogen's antigen.

According to at least some embodiments, any one of the foregoing therapeutic agents according to at least some embodiments of the present invention, including antibodies and antigen binding fragments and conjugates containing same, and/or alternative scaffolds, against any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins; LY6G6F, VSIG10, TMEM25 and/or LSR secreted or soluble form or ECD and/or variants, and/or orthologs, and/or conjugates thereof, can be used for adoptive immunotherapy. Immune tolerance or immunological tolerance is the process by which the immune system does not attack an antigen. It can be either 'natural' or 'self tolerance', where the body does not mount an immune response to self antigens, or 'induced tolerance', where tolerance to external antigens can be created by manipulating the immune system. It occurs in three forms: central tolerance, peripheral tolerance and acquired tolerance. Without wishing to be bound by a single theory, tolerance employs regulatory immune cells—including Tregs—that directly suppress autoreactive cells, as well as several other immune cell subsets with immunoregulatory properties—including CD8⁺ T cells and other types of CD4⁺ T cells (Tr1, Th3), in addition to natural killer (NK), NKT cells, dendritic cells (DC) and B cells.

Tolerance can be induced by blocking costimulation or upon engagement of a co-inhibitory B7 with its counter receptor. Transfer of tolerance involves isolation of the cells that have been induced for tolerance either in vivo (i.e. prior to cell isolation) or ex-vivo, enrichment and expansion of these cells ex vivo, followed by reinfusion of the expanded cells to the patient. This method can be used for treatment of autoimmune diseases as recited herein, immune related diseases as recited herein, transplantation and graft rejection. Thus, according to at least some embodiments, the invention provides methods for tolerance induction, comprising in vivo or ex vivo treatment administration of effective amount of any one of isolated soluble LY6G6F, VSIG10, TMEM25, LSR polypeptide, or a polypeptide comprising the extracellular domain of LY6G6F, VSIG10, TMEM25, LSR, or fragment thereof, or a fusion thereof to a heterologous sequence, and/or a polyclonal or monoclonal antibody or antigen binding fragments and conjugates containing same, and/or alternative scaffolds, specific to any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins, to a patient or to leukocytes isolated from the patient, in order to induce differentiation of tolerogenic regulatory cells, followed by ex-vivo enrichment and expansion of said cells and reinfusion of the tolerogenic regulatory cells to said patient.

According to at least some embodiments, the invention provides assays for detecting the presence of LY6G6F, VSIG10, TMEM25 and/or LSR proteins in vitro or in vivo in a biological sample or an individual, comprising contacting the sample with an antibody and/or antigen binding fragments and/or conjugates containing same, and/or alternative scaffolds, having specificity for LY6G6F, VSIG10, TMEM25 and/or LSR polypeptides, and detecting the binding of LY6G6F, VSIG10, TMEM25 and/or LSR protein in the sample and/or in the individual.

According to at least some embodiments, there is provided an assay for detecting the presence of any one of the polypep-

tides of any of SEQ ID NOs:1-8, 11-18, 47-50, 58, 143, or a variant thereof that is at least 95% identical thereto, in a sample.

According to at least some embodiments, there is provided a method for diagnosing a disease in a subject, comprising detecting in the subject or in a sample obtained from said subject any one of the polypeptides of any of SEQ ID NOs: 1-8, 11-18, 47-50, 58, 143, or a variant thereof that is at least 95% identical thereto, or fragments thereof.

Optionally detecting the polypeptide is performed in vivo or in vitro.

Optionally the detection is conducted by immunoassay.

Optionally the detection is conducted using antibodies or fragments as described herein.

According to at least some embodiments, the invention provides methods for detecting a disease, diagnosing a disease, monitoring disease progression or treatment efficacy or relapse of a disease, or selecting a therapy for a disease, detect cells affected by the foregoing disease, comprising detecting expression of a LY6G6F, VSIG10, TMEM25 and/or LSR, wherein the disease is selected from cancer, infectious disorder as recited herein, and/or immune related disorder.

According to one embodiment, detecting the presence of the polypeptide is indicative of the presence of the disease and/or its severity and/or its progress. According to another embodiment, a change in the expression and/or the level of the polypeptide compared to its expression and/or level in a healthy subject or a sample obtained therefrom is indicative of the presence of the disease and/or its severity and/or its progress. According to a further embodiment, a change in the expression and/or level of the polypeptide compared to its level and/or expression in said subject or in a sample obtained therefrom at earlier stage is indicative of the progress of the disease. According to still further embodiment, detecting the presence and/or relative change in the expression and/or level of the polypeptide is useful for selecting a treatment and/or monitoring a treatment of the disease.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 presents amino acid sequences of LY6G6F (FIG. 1A, SEQ ID NO:1), VSIG10 (FIG. 1B, SEQ ID NO:3, and 1C, SEQ ID NO:5), TMEM25 (FIG. 1D, SEQ ID NO:7), LSR (FIG. 1E (SEQ ID NO:11), 1F (SEQ ID NO:13), 1G (SEQ ID NO:15), 1H (SEQ ID NO:16), 1I (SEQ ID NO:17), and 1J (SEQ ID NO:18)) proteins, fragments, ECDs and the corresponding nucleic acid sequences encoding same. Amino acid residues corresponding to signal peptide (SP) appear in bold Italics. Ig-V and/or Ig-C domains are shown in boxes. Amino acid residues corresponding to transmembrane region (TM) appear in bold and underlined. Amino acid residues corresponding to alternative exons skipping in some of the isoforms (in FIGS. 1B, and 1E) appear in Italics and underlined. Nucleic acid sequence corresponding to alternative exons skipping variants of VSIG10 (skipping exon 3), and LSR (isoform-e, skipping exons 3, 4 and 5) appears in bold in FIGS. 1C, and 1I, respectively. Nucleic acid sequence corresponding to transmembrane region (TM) appears in bold and underlined in FIG. 1C. Nucleic acid sequence corresponding to signal peptide (SP) appears in bold Italics in FIGS. 1C, 1E, 1G, 1H, 1I, and 1J. TGA stop codon is highlighted in FIGS. 1C, and 1I.

FIG. 2 presents amino acid sequence comparison between: the VSIG10 variant SEQ ID NO:5 and the known VSIG10 protein, SEQ ID NO: 3 (genbank accession number NP_061959.2) (FIG. 2A); LSR_isoform-a, SEQ ID NO:11 and known LSR protein, genbank accession number

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NP_991403 SEQ ID NO:62 (FIG. 2B-1); LSR_isoform-a, SEQ ID NO:11 and known LSR protein, genbank accession number XP_002829104, SEQ ID NO:68 (FIG. 2B-2); LSR_isoform-b, SEQ ID NO:13 and known LSR protein, genbank accession number NP_057009, SEQ ID NO:63 (FIG. 2C-1); LSR_isoform-b, SEQ ID NO:13 and known LSR protein, genbank accession number BAC11614, SEQ ID NO:65 (FIG. 2C-2); LSR_isoform-c, SEQ ID NO:15 and known LSR protein, genbank accession number NP_991404, SEQ ID NO:66 (FIG. 2D-1); LSR_isoform-c, SEQ ID NO:15 and known LSR protein, genbank accession number XP_002829105.1, SEQ ID NO:69 (FIG. 2D-2); LSR_isoform-d, SEQ ID NO:16 and known LSR protein, genbank accession number NP_991404, SEQ ID NO:66 (FIG. 2E-1); LSR_isoform-d, SEQ ID NO:16 and known LSR protein, genbank accession number XP_002829105.1, SEQ ID NO:69 (FIG. 2E-2); LSR_isoform-e, SEQ ID NO:17 and known LSR protein, genbank accession number BAG59226.1, SEQ ID NO:67 (FIG. 2F); LSR_isoform-f, SEQ ID NO:18 and known LSR protein, genbank accession number NP_991403, SEQ ID NO:62 (FIG. 2G-1); LSR_isoform-f, SEQ ID NO:18 and known LSR protein, genbank accession number NP_991404, SEQ ID NO:66 (FIG. 2G-2). The sequence of the unique edge portions (unique junction) of the VSIG10 variant (SEQ ID NO:5) and LSR variant (SEQ ID NO:18) are bold and highlighted (FIGS. 2A and 2G, respectively).

FIG. 3 shows a scatter plot, demonstrating the expression of VSIG10 transcripts, that encode the VSIG10 proteins, on a virtual panel of all tissues and conditions using MED discovery engine, demonstrating differential expression of VSIG10 transcripts in several groups of cells from the immune system, mainly in leukocytes, and in various cancer conditions, such as CD10+ leukocytes from ALL and BM-CD34+ cells from AML.

FIG. 4 shows a scatter plot, demonstrating the expression of LSR transcripts, that encode the LSR proteins, on a virtual panel of all tissues and conditions using MED discovery engine, demonstrating differential expression of LSR transcripts in several groups of cells from the immune system, mainly in bone marrow cells, and in various cancerous conditions of tissues, such as in breast, lung, ovary, pancreas, prostate and skin cancers.

FIG. 5A presents LY6G6F human (SEQ ID NO: 1) and mouse (refNP_001156664.1, SEQ ID NO:29) amino acid sequence comparison. FIG. 5B presents VSIG10 human (SEQ ID NO: 3) and mouse (splD3YX43.2, SEQ ID NO:30) amino acid sequence comparison. FIG. 5C presents LSR human (SEQ ID NO:11) and either mouse (refNP_059101.1, SEQ ID NO:31) or mouse (refNP_001157656.1, SEQ ID NO:32) amino acid sequence comparison. FIG. 5D presents TMEM25 human (SEQ ID NO:7) and mouse (ref: 1cll4109, SEQ ID NO:28) amino acid sequence comparison.

FIG. 6 presents a table summarizing the primers which were used for cloning of LY6G6F transcript fused to EGFP. Gene specific sequences are shown in bold face; the restriction site extensions utilized for cloning purposes are in italic; and Kozak sequence are underlined.

FIG. 7 presents the DNA sequence of LY6G6F full length fused to EGFP. The gene specific sequence corresponding to the LY6G6F full length sequence is marked in bold faced, EGFP sequence is unbold italic underline.

FIG. 8 presents the amino acid sequence of the resulting LY6G6F full length fused to EGFP. The gene specific sequence corresponding to the full length sequence of LY6G6F is marked in bold faced; EGFP sequence is unbold italic underline.

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FIG. 9 presents cell localization of G6F_EGFP fusion protein transiently expressed in HEK293T cells. The image was obtained using the 40× objective of the confocal microscope.

FIG. 10 presents mouse ECDs fused to mouse IgG2a Fc as follows: mouse LY6G6F (also referred to herein as LY6G6F-Ig, FIG. 10A), mouse VSIG10 (FIG. 10B), mouse TMEM25 (also referred to herein as TMEM25-Ig, FIG. 10C) or mouse LSR (also referred to herein as LSR-Ig, FIG. 10D) ECD-IgG2aFc fused proteins (SEQ ID NOs: 23, 24, 25, or 26, respectively) Amino acid residues corresponding to signal peptide (SP) are shown in *Italics*. Amino acid residues corresponding to ECD sequence are underlined. Amino acid residues corresponding to mouse IgG2a Fc are shown in bold face (SEQ ID NO:27).

FIG. 11 presents amino acid sequences of human ECDs fused to human IgG1 Fc with the Cys at position 220 (according to full length human IgG1, position 5 in SEQ ID NO:70) replaced with a Ser (SEQ ID NO:156), as follows: human LY6G6F (FIG. 11A), human VSIG10 (FIG. 11B), human VSIG10-skipping exon 3 variant (FIG. 11C), human TMEM25 (FIG. 11D), human LSR isoform a (FIG. 11E), human LSR isoform b (FIG. 11F), human LSR isoform c (FIG. 11G), human LSR isoform d (FIG. 11H), human LSR isoform e (FIG. 11I), human LSR isoform f (FIG. 11J) ECD fused to human IgG1 Fc (SEQ ID NOs: 71-80, respectively) Amino acid residues corresponding to signal peptide (SP) are shown in bold *Italics*. Amino acid residues corresponding to human ECD sequence are underlined. Amino acid residues corresponding to human IgG1 Fc with the Cys at position 220 replaced with a Ser (SEQ ID NO:156) are unmarked.

FIG. 12 is a histogram showing over expression of the LSR transcripts detectable by or according to LSR_seg24-36_200-309/310_Amplicon (SEQ ID:140) in cancerous ovary samples relative to the normal samples.

FIG. 13 is a histogram showing over expression of the LSR transcripts detectable by or according to LSR_seg24-36_200-309/310_Amplicon (SEQ ID:140) in cancerous breast samples relative to the normal samples.

FIG. 14 is a histogram showing over expression of the LSR transcripts detectable by or according to LSR_seg24-36_200-309/310_Amplicon (SEQ ID:140) in cancerous lung samples relative to the normal samples.

FIG. 15 is a histogram showing over expression of the LSR transcripts detectable by or according to LSR_seg24-36_200-309/310_Amplicon (SEQ ID:140) in normal tissue samples relative to the ovary samples.

FIG. 16 is a histogram showing over expression of the LSR transcripts detectable by or according to LSR_seg24-36_200-309/310_Amplicon (SEQ ID:140) in cancerous kidney samples relative to the normal samples.

FIG. 17 is a histogram showing over expression of the LSR transcripts detectable by or according to LSR_seg24-36_200-309/310_Amplicon (SEQ ID:140) in cancerous liver samples relative to the normal samples.

FIG. 18 demonstrates Western Blot analysis of the expression of LSR_P5a_Flag_m protein (SEQ ID: 144) in stably transfected recombinant HEK293T cells, as detected with anti Flag (Sigma cat#A8592) (FIG. 18A) and anti LSR antibodies as follow: Abnova, cat#H00051599-B01P (FIG. 18B) Abcam, cat ab59646 (FIG. 18C) and Sigma cat#HPA007270 (FIG. 18D). Lane 1: HEK293T_pIRESpu3; lane 2: HEK293T_pIRESpu3_LSR_P5a_Flag.

FIG. 19 demonstrates the subcellular localization of LSR_P5a_Flag_m. LSR_P5a_Flag_m (SEQ ID NO: 144) is localized mainly to the cell cytoplasm, but can also be detected on the cell surface as detected with anti Flag (Sigma cat#A9594) (FIG. 19A) and anti LSR antibodies as follows:

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Abcam, cat ab59646 (FIG. 19B) Abnova, cat#H00051599-B01P (FIG. 19C) and Sigma cat#HPA007270 (FIG. 19D).

FIG. 20 demonstrates the endogenous expression of LSR in various cell lines. A band at 72 kDa corresponding to LSR was detected with anti LSR antibody in extracts of (1) Caov3, (2) ES2, (3) OV-90, (4) OVCAR3, (5) SK-OV3, (6) TOV112D, (7) CaCo2, (8) HeLa, (9) Hep G2, (10) MCF-7, (11) SkBR3 and (12) 293T_LSR_P5a_Flag (FIG. 20A). Anti GAPDH (Abcam cat#ab9484) served as a loading control (FIG. 20B).

FIG. 21 is a histogram showing expression of TMEM25 transcripts detectable by or according to seg21-27—TMEM25_seg_21-27_200-344/346_Amplicon (SEQ ID NO: 123) in normal and cancerous Breast tissues.

FIG. 22 is a histogram showing expression of TMEM25 transcripts detectable by or according to seg21-27—TMEM25_seg_21-27_200-344/346_Amplicon (SEQ ID NO: 123) in different normal tissues.

FIG. 23 demonstrates Western blot results showing (A) specific interaction between Rabbit anti TMEM25 antibodies and TMEM25_P5 protein (SEQ ID NO: 7) and TMEM25_P5_Flag (SEQ ID NO: 129), but not HEK_293T_pRp3. (B) specific interaction between TMEM25_P5_Flag protein (SEQ ID NO: 129) and anti-Flag antibodies. Lane1: HEK293T_pIRESpu3; lane 2: HEK293T_pIRESpu3_TMEM25-P5, lane 3: HEK293T_pIRESpu3_TMEM25-P5-Flag.

FIG. 24 presents the cell surface localization of TMEM25_P5 (SEQ ID NO:132) (FIG. 24A) and TMEM25_P5_Flag (SEQ ID NO: 129) (FIG. 24B) using anti TMEM25 Abs. FIG. 24C demonstrate TMEM25_P5_Flag (SEQ ID NO: 129) localization using anti flag Abs (Sigma, catalog number: A9594).

FIG. 25 demonstrates that anti TMEM25 antibodies bind to the full length TMEM25 protein, in HEK293T recombinant cells expressing TMEM25_P5_Flag protein (1:2250) (FIG. 25A), as compared to mouse serum (1:2250) (FIG. 25B) used as a negative control, indicating membrane localization of TMEM25 protein.

FIG. 26 presents Western Blot results showing the expression of endogenous TMEM25 protein in various cell lines: (1): HEK293T_pIRESpu3, (2) HEK293T_pIRESpu3_TMEM25-P5-Flag, (3) KARPAS, (4) G-361, (5) RPMI8226, (6) DAUDI, (7) Jurkat.

FIG. 27 demonstrates specific knockdown of TMEM25_P5_Flag protein (SEQ ID NO: 129) in HEK293T cells stably expressing TMEM25_P5_Flag (SEQ ID NO 129) transfected with TMEM25_P5 siRNA (L-018183-00-0005, Dharmacon) (Lane 2) compared to HEK293T cells stably expressing TMEM25_P5_FLAG transfected with Scrambled-SiRNA (Lane 1) (Dharmacon, D-001810-10-05), using anti TMEM25 antibodies (Sigma, cat#HPA012163).

FIG. 28 demonstrates that anti LSR (Cat no. ab59646, Abcam) in sections of positive control cell line (LSR_P5a_Flag_m transfected HEK293T cells (column 1, panels A, C and E) shows specific immunoreactivity in a dose dependent concentrations of 3, 1 and 0.3 ug/ml respectively, as compared to the negative control cell line empty vector HEK293T cells (column 2, panels B, D and F), in pH 9 antigen retrieval method.

FIG. 29 demonstrates that anti TMEM25 (Cat no. HPA012163, Sigma) in sections of positive control cell line TMEM25_P5_Flag transfected HEK293T cells (column 1, panels A, C and E) shows specific immunoreactivity in a dose dependent concentrations of 3, 1 and 0.3 ug/ml respectively,

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as compared to the negative control cell line empty vector HEK293T cells (column 2 panels B, D and F), in pH 9 antigen retrieval method.

FIG. 30A-F shows the in vitro inhibitory effect of soluble LY6G6F-Ig (SEQ ID NO:23), TMEM25-Ig (SEQ ID NO:25) and LSR-Ig (SEQ ID NO:26) on mouse T cells activation. Activation of T cells isolated from spleens of D011.10 mice was induced with 20 ug/ml (FIGS. 30A-C, E) or 2 ug/ml (FIGS. D and F) OVA323-339 in the presence of irradiated splenocytes from Balb/c mice that serve as APCs. In these studies CTLA4-Ig or B7-H4-Ig were used as positive controls while mouse IgG2a was used as Ig control.

FIG. 31 shows the in vitro inhibitory effect of bead bound LSR-Ig (SEQ ID NO:26) on T cell proliferation induced by anti-CD3 and anti-CD28 coated beads.

FIG. 32 shows the effect of LY6G6F, VSIG10, TMEM25 and LSR fusion proteins (SEQ ID NO:23-26, respectively) on CD4 T cell activation, as manifested by reduced IFN γ secretion (A) and reduced expression of the activation marker CD69 (B). Each bar is the mean of duplicate cultures, the error bars indicating the standard deviation (Student t-test, *P<0.05, **p<0.01, compared with control mIgG2a.

FIG. 33 shows the effect of stimulator cells (a murine thymoma cell line, Bw5147, which were engineered to express membrane-bound anti-human CD3 antibody fragments) expressing the cDNAs encoding human LY6G6F, TMEM25 or LSR (SEQ ID NOs: 1, 7 or 11, respectively) on the proliferation (CPM) of bulk human T cells (FIG. 33A), CD4+ human T cells (FIG. 33B), CD8+ human T cells (FIG. 33C), or naive CD4CD45RA+ human T cells (FIG. 33D). Results are displayed as the mean \pm SEM of 6 (FIG. 337A) or 3 (FIGS. 33B, C, and D) experiments. *P<0.05, **p<0.01, ***p<0.001, and #p<0.0001 (Students T-test) represent significantly different results compared to empty vector.

FIG. 34 shows the therapeutic effect of LSR-Ig (SEQ ID NO:26) or TMEM25-Ig (SEQ ID NO:25) treatment in the PLP139-151-induced R-EAE model in SJL mice. LSR-Ig (SEQ ID NO:26) or TMEM25-Ig (SEQ ID NO:25) were administered in a therapeutic mode from the onset of disease remission (day 18), at 100 microg/mouse i.p. 3 times per week for two weeks. Therapeutic effects of LSR-Ig and TMEM25-Ig on clinical symptoms are demonstrated as reduction in Mean Clinical Score (FIG. 34A). In addition, LSR-Ig and TMEM25-Ig treatment inhibited DTH responses to inducing epitope (PLP139-151) or spread epitope (PLP178-191), on day 35 after R-EAE induction (FIG. 34B). In this study the effect of LSR-Ig or TMEM25-Ig was studied in comparison to mIgG2a Ig negative control and CTLA4-Ig positive control that were administered at a similar regimen as the test proteins.

FIG. 35 shows the dose dependency and mode of action of the effect of TMEM25-Ig (SEQ ID NO:25) in the R-EAE model in SJL mice. In this study, treatments were given from onset of disease remission (day 19) at 100, 30 or 10 microg/mouse i.p. 3 times per week for two weeks, as compared to 100 microg/mouse IgG2a control that was given at a similar schedule. shown are effects of TMEM25-Ig treatment on disease course (FIG. 35A), DTH responses to spread epitopes PLP178-191 and MBP84-104 on days 45 and 76 post R-EAE induction (FIG. 35B), ex-vivo recall responses of splenocytes isolated on day 45 and 75 post disease induction (FIG. 35C) and LN cells isolated on day 45 post disease induction (FIG. 35D) as manifested by the effect of TMEM25-Ig treatment on cell proliferation and cytokine secretion (IFN γ , IL-17, IL-10 and IL-4). The effect of TMEM25-Ig on cell counts in the spleen, lymph nodes and CNS as well as the different linages

present in the CNS upon treatment with TMEM25-Ig at 100 ug/dose is shown in FIG. 35E.

FIG. 36 shows the therapeutic effect of VSIG10-Ig (SEQ ID NO:24) treatment in the PLP139-151-induced R-EAE model in SJL mice. VSIG10-Ig (SEQ ID NO:24) was administered in a therapeutic mode from the onset of disease remission (day 19), at 100 microg/mouse i.p. 3 times per week for two weeks. Therapeutic effects of VSIG10-Ig on clinical symptoms is demonstrated as reduction in Mean Clinical Score (FIG. 36A). In addition, VSIG10-Ig treatment inhibited DTH responses to spread epitopes (PLP178-191 and MBP MBP84-104), on days 45 and 76 after R-EAE induction (FIG. 36B). Also shown is the effect of VSIG10-Ig on ex-vivo recall responses of splenocytes isolated on day 45 and 75 post disease induction (FIG. 36C) and LN cells isolated on day 45 post disease induction (FIG. 36D) as manifested by the effect of VSIG10-Ig treatment on cell proliferation and cytokine secretion (IFN γ , IL-17, IL-10 and IL-4). The effect of VSIG10-Ig on cell counts in the spleen, lymph nodes and CNS as well as the different lineages present within each of these tissues upon treatment with VSIG10-Ig at 100 ug/dose is shown in FIG. 36E. In this study the effect of VSIG10-Ig was studied in comparison to mlgG2a Ig control that was administered at similar dose and regimen as VSIG10-Ig.

FIG. 37 shows the therapeutic effect of LSR-Ig (SEQ ID NO:26) administered at 100 microg/mouse, i.p. 3 times per week for 10 days in collagen induced arthritis (CIA) model of Rheumatoid Arthritis. Measured are clinical score (A) paw swelling (B) and histological damage (C) CTLA4-Ig, (100 microg/mouse) and TNFR-Ig (etanercept) were used as a positive control while mlgG2a Ig control (100 microg/mouse) was used as negative control.

FIG. 38 shows the therapeutic effect of LY6G6F-Ig (SEQ ID NO:23) administered at 25 mg/kg, i.p. 3 times per week for 2 weeks in collagen induced arthritis (CIA) model of Rheumatoid Arthritis, with measurements given according to clinical scores.

For FIGS. 12-17, 21, 22, division was made into separate parts "A", "B" and so forth for reasons of space only, so as to be able to show all results.

DETAILED DESCRIPTION OF THE INVENTION

The present invention, in at least some embodiments, relates to any one of the proteins referred to as LY6G6F, VSIG10, TMEM25 and/or LSR, and its corresponding nucleic acid sequence, and portions and variants thereof and fusion proteins and conjugates containing, and/or polyclonal and monoclonal antibodies and/or antigen binding fragments and/or conjugates containing same, and/or alternative scaffolds thereof that bind LY6G6F, VSIG10, TMEM25 and/or LSR and/or portions and/or variants thereof, and the use thereof as a therapeutic and/or diagnostic agent, and various uses as described herein.

US Patent Application Nos. US2009117566, US20090017473, and other family members, assigned to GENENTECH INC., disclose a 382 amino acid LY6G6F protein sequence (DNA234441, tumor-associated antigenic target (TAT) TAT201, SEQ ID NO:92 therein) having a trans-membrane domain between residues 234-254 and 354-374. '566, '473, applications and other applications from this patent family disclose that TAT201 is over expressed in colon and rectal cancers. PCT Application Nos WO2003083074 and WO2004046342 disclose a 382 amino acid LY6G6F protein sequence as one of many genes that are over expressed in colon cancer cells. These patent applications further purportedly relate to methods of use of LY6G6F for detecting and

treating colon cancer. However, these patent applications do not teach or suggest or provide any incentive that would direct a skilled artisan to use antibodies specific to the LY6G6F and/or LY6G6F ECD for treatment and/or diagnosis of cancer other than colorectal cancer, and/or infectious disorders, and/or immune related disorders. These patent applications do not describe LY6G6F ECD and do not teach or suggest or provide any incentive that would direct a skilled artisan to use the LY6G6F ECD for treatment of cancer and/or infectious disorders, and/or immune related disorders.

TMEM25 is disclosed in PCT Application Nos WO9958642 and WO2003087300, and US Patent Application Nos. US2007041963 and US2005202526, as one of many (hundreds to thousands) proteins, useful for diagnosing, preventing, and treating disorders associated with an abnormal expression or activity of these proteins. However, these applications do not teach or suggest or provide any incentive that would direct a skilled artisan to use antibodies specific to the TMEM25 and/or TMEM25 ECD for treatment and/or diagnosis of cancer and/or infectious disorders, and/or immune related disorders. TMEM25 is also disclosed in US Patent Application No. US2004010134, as one of hundreds of albumin fusion proteins, useful for diagnosing, treating, preventing or ameliorating diseases or disorders e.g. cancer, anemia, arthritis, asthma, inflammatory bowel disease or Alzheimer's disease. However, this application does not teach or suggest or provide any incentive that would direct a skilled artisan to use antibodies specific to the TMEM25 and/or TMEM25 ECD for treatment and/or diagnosis of cancer and/or infectious disorders, and/or immune related disorders. TMEM25 is also described in Doolan P, et al., Tumour Biol. 2009, 30(4):200-9 as a favourable prognostic and predictive biomarker for breast cancer diagnosis. However, this publication does not teach or suggest or provide any incentive that would direct a skilled artisan to use the antibodies specific to TMEM25 and/or TMEM25 ECD for treatment of cancer and/or infectious disorders, and/or immune related disorders.

In order that the present invention in various embodiments may be more readily understood, certain terms are first defined. Additional definitions are set forth throughout the detailed description.

As used herein the term "isolated" refers to a compound of interest (for example a polynucleotide or a polypeptide) that is in an environment different from that in which the compound naturally occurs e.g. separated from its natural milieu such as by concentrating a peptide to a concentration at which it is not found in nature. "Isolated" includes compounds that are within samples that are substantially enriched for the compound of interest and/or in which the compound of interest is partially or substantially purified.

An "immune cell" refers to any cell from the hemopoietic origin including but not limited to T cells, B cells, monocytes, dendritic cells, and macrophages.

As used herein, the term "polypeptide" refers to a chain of amino acids of any length, regardless of modification (e.g., phosphorylation or glycosylation).

As used herein, a "costimulatory polypeptide" or "costimulatory molecule" is a polypeptide that, upon interaction with a cell-surface molecule on T cells, modulates T cell responses.

As used herein, a "costimulatory signaling" is the signaling activity resulting from the interaction between costimulatory polypeptides on antigen presenting cells and their receptors on T cells during antigen-specific T cell responses. Without wishing to be limited by a single hypothesis, the antigen-specific T cell response is believed to be mediated by two

signals: 1) engagement of the T cell Receptor (TCR) with antigenic peptide presented in the context of MHC (signal 1), and 2) a second antigen-independent signal delivered by contact between different costimulatory receptor/ligand pairs (signal 2). Without wishing to be limited by a single hypothesis, this “second signal” is critical in determining the type of T cell response (activation vs inhibition) as well as the strength and duration of that response, and is regulated by both positive and negative signals from costimulatory molecules, such as the B7 family of proteins.

As used herein, the term “B7” polypeptide means a member of the B7 family of proteins that costimulate T cells including, but not limited to B7-1, B7-2, B7-DC, B7-H5, B7-H1, B7-H2, B7-H3, B7-H4, B7-H6, B7-S3 and biologically active fragments and/or variants thereof. Representative biologically active fragments include the extracellular domain or fragments of the extracellular domain that costimulate T cells.

As used herein, a “variant” polypeptide contains at least one amino acid sequence alteration as compared to the amino acid sequence of the corresponding wild-type polypeptide.

As used herein, “conservative” amino acid substitutions are substitutions wherein the substituted amino acid has similar structural or chemical properties. As used herein, the term “host cell” refers to prokaryotic and eukaryotic cells into which a recombinant vector can be introduced.

As used herein, the term “an edge portion” or “a new junction” refers to a connection between two portions of a splice variant according to the present invention that were not joined in the wild type or known protein. An edge may optionally arise due to a join between the above “known protein” portion of a variant and the tail, for example, and/or may occur if an internal portion of the wild type sequence is no longer present, such that two portions of the sequence are now contiguous in the splice variant that were not contiguous in the known protein. A “bridge” may optionally be an edge portion as described above, but may also include a join between a head and a “known protein” portion of a variant, or a join between a tail and a “known protein” portion of a variant, or a join between an insertion and a “known protein” portion of a variant.

In some embodiments, a bridge between a tail or a head or a unique insertion, and a “known protein” portion of a variant, comprises at least about 10 amino acids, or in some embodiments at least about 20 amino acids, or in some embodiments at least about 30 amino acids, or in some embodiments at least about 40 amino acids, in which at least one amino acid is from the tail/head/insertion and at least one amino acid is from the “known protein” portion of a variant. In some embodiments, the bridge may comprise any number of amino acids from about 10 to about 40 amino acids (for example, 10, 11, 12, 13 . . . 37, 38, 39, 40 amino acids in length, or any number in between).

It should be noted that a bridge cannot be extended beyond the length of the sequence in either direction, and it should be assumed that every bridge description is to be read in such manner that the bridge length does not extend beyond the sequence itself.

Furthermore, bridges are described with regard to a sliding window in certain contexts below. For example, certain descriptions of the bridges feature the following format: a bridge between two edges (in which a portion of the known protein is not present in the variant) may optionally be described as follows: a bridge portion of CONTIG-NAME_P1 (representing the name of the protein), comprising a polypeptide having a length “n”, wherein n is at least about 10 amino acids in length, optionally at least about 20

amino acids, at least about 30 amino acids, at least about 40 amino acids, or at least about 50 amino acids in length, wherein at least two amino acids comprise XX (2 amino acids in the center of the bridge, one from each end of the edge), having a structure as follows (numbering according to the sequence of CONTIG-NAME_PD: a sequence starting from any of amino acid numbers 49-x to 49 (for example); and ending at any of amino acid numbers 50+((n-2)-x) (for example), in which x varies from 0 to n-2. In this example, it should also be read as including bridges in which n is any number of amino acids between 10-50 amino acids in length. Furthermore, the bridge polypeptide cannot extend beyond the sequence, so it should be read such that 49-x (for example) is not less than 1, nor 50+((n-2)-x) (for example) greater than the total sequence length.

The term “cancer” as used herein should be understood to encompass any neoplastic disease (whether invasive or metastatic) which is characterized by abnormal and uncontrolled cell division causing malignant growth or tumor. Non-limiting examples of cancer which may be treated with a compound according to at least some embodiments of the present invention are solid tumors, sarcomas and hematological malignancies, including but not limited to breast cancer (e.g. breast carcinoma), cervical cancer, ovary cancer (ovary carcinoma), endometrial cancer, melanoma, bladder cancer (bladder carcinoma), lung cancer (e.g. adenocarcinoma and non-small cell lung cancer), pancreatic cancer (e.g. pancreatic carcinoma such as exocrine pancreatic carcinoma), colon cancer (e.g. colorectal carcinoma, such as colon adenocarcinoma and colon adenoma), prostate cancer including the advanced disease, hematopoietic tumors of lymphoid lineage (e.g. leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, B-cell lymphoma, Burkitt’s lymphoma, multiple myeloma, Hodgkin’s lymphoma, Non-Hodgkin’s lymphoma), myeloid leukemia (for example, acute myelogenous leukemia (AML), chronic myelogenous leukemia), thyroid cancer, thyroid follicular cancer, myelodysplastic syndrome (MDS), tumors of mesenchymal origin (e.g. fibrosarcomas and rhabdomyosarcomas), melanoma, uveal melanoma, teratocarcinoma, neuroblastoma, glioma, glioblastoma, benign tumor of the skin (e.g. keratoacanthomas), renal cancer, anaplastic large-cell lymphoma, esophageal squamous cells carcinoma, hepatocellular carcinoma, follicular dendritic cell carcinoma, intestinal cancer, muscle-invasive cancer, seminal vesicle tumor, epidermal carcinoma, spleen cancer, bladder cancer, head and neck cancer, stomach cancer, liver cancer, bone cancer, brain cancer, cancer of the retina, biliary cancer, small bowel cancer, salivary gland cancer, cancer of uterus, cancer of testicles, cancer of connective tissue, prostatic hypertrophy, myelodysplasia, Waldenstrom’s macroglobinemia, nasopharyngeal, neuroendocrine cancer, myelodysplastic syndrome, mesothelioma, angiosarcoma, Kaposi’s sarcoma, carcinoid, oesophagogastric, fallopian tube cancer, peritoneal cancer, papillary serous mullerian cancer, malignant ascites, gastrointestinal stromal tumor (GIST), and a hereditary cancer syndrome such as Li-Fraumeni syndrome and Von Hippel-Lindau syndrome (VHL), and wherein the cancer may be non-metastatic, invasive or metastatic.

According to at least some preferred embodiments of the present invention, the cancer is selected from the group consisting of melanoma, cancers of liver, renal, brain, breast, colon, lung, ovary, pancreas, prostate, stomach, multiple myeloma and hematopoietic cancer, including but not limited to lymphoma (Hodgkin’s and non Hodgkin’s), acute and chronic lymphoblastic leukemia and acute and chronic myeloid leukemia, and wherein the cancer may be non-metastatic, invasive or metastatic.

The term "autoimmune disease" as used herein should be understood to encompass any autoimmune disease and chronic inflammatory conditions. According to at least some embodiments of the invention, the autoimmune diseases should be understood to encompass any disease disorder or condition selected from the group including but not limited to multiple sclerosis, including relapsing-remitting multiple sclerosis, primary progressive multiple sclerosis, and secondary progressive multiple sclerosis; psoriasis; rheumatoid arthritis; psoriatic arthritis, systemic lupus erythematosus (SLE); ulcerative colitis; Crohn's disease; benign lymphocytic angiitis, thrombocytopenic purpura, idiopathic thrombocytopenia, idiopathic autoimmune hemolytic anemia, pure red cell aplasia, Sjogren's syndrome, rheumatic disease, connective tissue disease, inflammatory rheumatism, degenerative rheumatism, extra-articular rheumatism, juvenile rheumatoid arthritis, arthritis uratica, muscular rheumatism, chronic polyarthritis, cryoglobulinemic vasculitis, ANCA-associated vasculitis, antiphospholipid syndrome, myasthenia gravis, autoimmune haemolytic anaemia, Guillain-Barre syndrome, chronic immune polyneuropathy, autoimmune thyroiditis, insulin dependent diabetes mellitus, type I diabetes, Addison's disease, membranous glomerulonephropathy, Goodpasture's disease, autoimmune gastritis, autoimmune atrophic gastritis, pernicious anaemia, pemphigus, pemphigus vulgaris, cirrhosis, primary biliary cirrhosis, dermatomyositis, polymyositis, fibromyositis, myogelosis, celiac disease, immunoglobulin A nephropathy, Henoch-Schönlein purpura, Evans syndrome, atopic dermatitis, psoriasis, psoriasis arthropathica, Graves' disease, Graves' ophthalmopathy, scleroderma, systemic scleroderma, progressive systemic scleroderma, asthma, allergy, primary biliary cirrhosis, Hashimoto's thyroiditis, primary myxedema, sympathetic ophthalmia, autoimmune uveitis, hepatitis, chronic action hepatitis, collagen diseases, ankylosing spondylitis, periarthritis humeroscapularis, panarteritis nodosa, chondrocalcinosis, Wegener's granulomatosis, microscopic polyangiitis, chronic urticaria, bullous skin disorders, pemphigoid, atopic eczema, Devic's disease, childhood autoimmune hemolytic anemia, Refractory or chronic Autoimmune Cytopenias, Prevention of development of Autoimmune Anti-Factor VIII Antibodies in Acquired Hemophilia A, Cold Agglutinin Disease, Neuromyelitis Optica, Stiff Person Syndrome, gingivitis, periodontitis, pancreatitis, myocarditis, vasculitis, gastritis, gout, gouty arthritis, and inflammatory skin disorders, selected from the group consisting of psoriasis, atopic dermatitis, eczema, rosacea, urticaria, and acne, normocomplementemic urticarial vasculitis, pericarditis, myositis, anti-synthetase syndrome, scleritis, macrophage activation syndrome, Bechet's Syndrome, PAPA Syndrome, Blau's Syndrome, gout, adult and juvenile Still's disease, cryopyrinopathy, Muckle-Wells syndrome, familial cold-induced auto-inflammatory syndrome, neonatal onset multisystemic inflammatory disease, familial Mediterranean fever, chronic infantile neurologic, cutaneous and articular syndrome, systemic juvenile idiopathic arthritis, Hyper IgD syndrome, Schnitzler's syndrome, autoimmune retinopathy, age-related macular degeneration, atherosclerosis, chronic prostatitis and TNF receptor-associated periodic syndrome (TRAPS).

Optionally and preferably, the autoimmune disease includes but is not limited to any of the types and subtypes of any of multiple sclerosis, rheumatoid arthritis, type I diabetes, psoriasis, systemic lupus erythematosus, inflammatory bowel disease, uveitis, or Sjogren's syndrome.

As used herein, "multiple sclerosis" comprises one or more of multiple sclerosis, benign multiple sclerosis, relapsing remitting multiple sclerosis, secondary progressive multiple

sclerosis, primary progressive multiple sclerosis, progressive relapsing multiple sclerosis, chronic progressive multiple sclerosis, transitional/progressive multiple sclerosis, rapidly worsening multiple sclerosis, clinically-definite multiple sclerosis, malignant multiple sclerosis, also known as Marburg's Variant, and acute multiple sclerosis. Optionally, "conditions relating to multiple sclerosis" include, e.g., Devic's disease, also known as Neuromyelitis Optica; acute disseminated encephalomyelitis, acute demyelinating optic neuritis, demyelinating transverse myelitis, Miller-Fisher syndrome, encephalomyelradiculoneuropathy, acute demyelinating polyneuropathy, tumefactive multiple sclerosis and Balo's concentric sclerosis.

As used herein, "rheumatoid arthritis" comprises one or more of rheumatoid arthritis, gout and pseudo-gout, juvenile idiopathic arthritis, juvenile rheumatoid arthritis, Still's disease, ankylosing spondylitis, rheumatoid vasculitis. Optionally, conditions relating to rheumatoid arthritis include, e.g., osteoarthritis, sarcoidosis, Henoch-Schönlein purpura, Psoriatic arthritis, Reactive arthritis, Spondyloarthropathy, septic arthritis, Haemochromatosis, Hepatitis, vasculitis, Wegener's granulomatosis, Lyme disease, Familial Mediterranean fever, Hyperimmunoglobulinemia D with recurrent fever, TNF receptor associated periodic syndrome, and Enteropathic arthritis associated with inflammatory bowel disease.

As used herein, "Uveitis" comprises one or more of uveitis, anterior uveitis (or iridocyclitis), intermediate uveitis (pars planitis), posterior uveitis (or chorioretinitis) and the panuveitic form.

As used herein, "inflammatory bowel disease" comprises one or more of inflammatory bowel disease Crohn's disease, ulcerative colitis (UC), Collagenous colitis, Lymphocytic colitis, Ischaemic colitis, Diversion colitis, Behçet's disease, Indeterminate colitis.

As used herein, "psoriasis" comprises one or more of psoriasis, Nonpustular Psoriasis including Psoriasis vulgaris and Psoriatic erythroderma (erythrodermic psoriasis), Pustular psoriasis including Generalized pustular psoriasis (pustular psoriasis of von Zumbusch), Pustulosis palmaris et plantaris (persistent palmoplantar pustulosis, pustular psoriasis of the Barber type, pustular psoriasis of the extremities), Annular pustular psoriasis, Acrodermatitis continua, Impetigo herpetiformis. Optionally, conditions relating to psoriasis include, e.g., drug-induced psoriasis, Inverse psoriasis, Napkin psoriasis, Seborrheic-like psoriasis, Guttate psoriasis, Nail psoriasis, Psoriatic arthritis.

As used herein, "type 1 diabetes" comprises one or more of type 1 diabetes, insulin-dependent diabetes mellitus, idiopathic diabetes, juvenile type 1 diabetes, maturity onset diabetes of the young, latent autoimmune diabetes in adults, gestational diabetes. Conditions relating to type 1 diabetes include, neuropathy including polyneuropathy, mononeuropathy, peripheral neuropathy and autonomic neuropathy; eye complications: glaucoma, cataracts, retinopathy.

As used herein, "Sjogren's syndrome" comprises one or more of Sjogren's syndrome, Primary Sjogren's syndrome and Secondary Sjogren's syndrome, as well as conditions relating to Sjogren's syndrome including connective tissue disease, such as rheumatoid arthritis, systemic lupus erythematosus, or scleroderma. Other complications include pneumonia, pulmonary fibrosis, interstitial nephritis, inflammation of the tissue around the kidney's filters, glomerulonephritis, renal tubular acidosis, carpal tunnel syndrome, peripheral neuropathy, cranial neuropathy, primary biliary cirrhosis (PBC), cirrhosis, Inflammation in the esophagus, stomach, pancreas, and liver (including hepatitis),

Polymyositis, Raynaud's phenomenon, Vasculitis, Autoimmune thyroid problems, lymphoma.

As used herein, "systemic lupus erythematosus", comprises one or more of systemic lupus erythematosus, discoid lupus, lupus arthritis, lupus pneumonitis, lupus nephritis. Conditions relating to systemic lupus erythematosus include osteoarticular tuberculosis, antiphospholipid antibody syndrome, inflammation of various parts of the heart, such as pericarditis, myocarditis, and endocarditis, Lung and pleura inflammation, pleuritis, pleural effusion, chronic diffuse interstitial lung disease, pulmonary hypertension, pulmonary emboli, pulmonary hemorrhage, and shrinking lung syndrome, lupus headache, Guillain-Barré syndrome, aseptic meningitis, demyelinating syndrome, mononeuropathy, mononeuritis multiplex, myasthenia gravis, myelopathy, cranial neuropathy, polyneuropathy, vasculitis.

The term "immune related disease (or disorder or condition)" as used herein should be understood to encompass any disease disorder or condition selected from the group including but not limited to autoimmune diseases, inflammatory disorders and immune disorders associated with graft transplantation rejection, such as acute and chronic rejection of organ transplantation, allogenic stem cell transplantation, autologous stem cell transplantation, bone marrow transplantation, and graft versus host disease.

As used herein the term "inflammatory disorders" and/or "inflammation", used interchangeably, includes inflammatory abnormalities characterized by dysregulated immune response to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammatory disorders underlie a vast variety of human diseases. Non-immune diseases with etiological origins in inflammatory processes include cancer, atherosclerosis, and ischaemic heart disease. Examples of disorders associated with inflammation include: Chronic prostatitis, Glomerulonephritis, Hypersensitivities, Pelvic inflammatory disease, Reperfusion injury, Sarcoidosis, Vasculitis, Interstitial cystitis, normocomplementemic urticarial vasculitis, pericarditis, myositis, anti-synthetase syndrome, scleritis, macrophage activation syndrome, Bechet's Syndrome, PAPA Syndrome, Blau's Syndrome, gout, adult and juvenile Still's disease, cryopyrinopathy, Muckle-Wells syndrome, familial cold-induced auto-inflammatory syndrome, neonatal onset multisystemic inflammatory disease, familial Mediterranean fever, chronic infantile neurologic, cutaneous and articular syndrome, systemic juvenile idiopathic arthritis, Hyper IgD syndrome, Schnitzler's syndrome, TNF receptor-associated periodic syndrome (TRAPSP), gingivitis, periodontitis, hepatitis, cirrhosis, pancreatitis, myocarditis, vasculitis, gastritis, gout, gouty arthritis, and inflammatory skin disorders, selected from the group consisting of psoriasis, atopic dermatitis, eczema, rosacea, urticaria, and acne.

As used herein the term "infectious disorder and/or disease" and/or "infection", used interchangeably, includes any disorder, disease and/or condition caused by presence and/or growth of pathogenic biological agent in an individual host organism. As used herein the term "infection" comprises the disorder, disease and/or condition as above, exhibiting clinically evident illness (i.e., characteristic medical signs and/or symptoms of disease) and/or which is asymptomatic for much or all of its course. As used herein the term "infection" also comprises disorder, disease and/or condition caused by persistence of foreign antigen that lead to exhaustion T cell phenotype characterized by impaired functionality which is manifested as reduced proliferation and cytokine production. As used herein the term "infectious disorder and/or disease" and/or "infection", further includes any of the below listed

infectious disorders, diseases and/or conditions, caused by a bacterial infection, viral infection, fungal infection and/or parasite infection.

As used herein the term "viral infection" comprises any infection caused by a virus, optionally including but not limited to Retroviridae (e.g., human immunodeficiency viruses, such as HIV-1 or HIV-2, acquired immune deficiency (AIDS) also referred to as HTLV-III, LAV or HTLV-III/LAV, or HIV-III; and other isolates, such as HIV-LP; Picornaviridae (e.g., polio viruses, hepatitis A virus; enteroviruses, human coxsackie viruses, rhinoviruses, echoviruses); Calciviridae (e.g., strains that cause gastroenteritis); Togaviridae (e.g., equine encephalitis viruses, rubella viruses); Flaviridae (e.g., dengue viruses, encephalitis viruses, yellow fever viruses); Coronaviridae (e.g., coronaviruses); Rhabdoviridae (e.g., vesicular stomatitis viruses, rabies viruses); Filoviridae (e.g., ebola viruses); Paramyxoviridae (e.g., parainfluenza viruses, mumps virus, measles virus, respiratory syncytial virus); Orthomyxoviridae (e.g., influenza viruses); Bunyaviridae (e.g., Hantaan viruses, bunya viruses, phleboviruses and Nairo viruses); Arenaviridae (hemorrhagic fever virus); Reoviridae (e.g., reoviruses, orbiviruses and rotaviruses); Birnaviridae; Hepadnaviridae (Hepatitis B virus); Parvoviridae (parvoviruses); Papovaviridae (papilloma viruses, polyoma viruses); Adenoviridae (most adenoviruses); Herpesviridae (herpes simplex virus (HSV) 1 and 2, varicella zoster virus, cytomegalovirus (CMV), herpes viruses); Poxviridae (variola viruses, vaccinia viruses, pox viruses); and Iridoviridae (e.g., African swine fever virus); and unclassified viruses (e.g., the etiological agents of Spongiform encephalopathies, the agent of delta hepatitis (thought to be a defective satellite of hepatitis B virus), the agents of non-A, non-B hepatitis (class 1-internally transmitted; class 2-parenterally transmitted (i.e., Hepatitis C); Norwalk and related viruses, and astroviruses) as well as Severe acute respiratory syndrome virus and respiratory syncytial virus (RSV).

As used herein the term "fungal infection" comprises any infection caused by a fungi, optionally including but not limited to *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Chlamydia trachomatis*, *Candida albicans*.

As used herein the term "parasite infection" comprises any infection caused by a parasite, optionally including but not limited to protozoa, such as Amebae, Flagellates, *Plasmodium falciparum*, *Toxoplasma gondii*, *Ciliates*, *Coccidia*, *Microsporidia*, *Sporozoa*; *helminthes*, *Nematodes* (Roundworms), *Cestodes* (Tapeworms), *Trematodes* (Flukes), Arthropods, and aberrant proteins known as prions.

An infectious disorder and/or disease caused by bacteria may optionally comprise one or more of Sepsis, septic shock, sinusitis, skin infections, pneumonia, bronchitis, meningitis, Bacterial vaginosis, Urinary tract infection (UTI), Bacterial gastroenteritis, Impetigo and erysipelas, Erysipelas, Cellulitis, anthrax, whooping cough, Lyme disease, Brucellosis, enteritis, acute enteritis, Tetanus, diphtheria, Pseudomembranous colitis, Gas gangrene, Acute food poisoning, Anaerobic cellulitis, Nosocomial infections, Diarrhea, Meningitis in infants, Traveller's diarrhea, Hemorrhagic colitis, Hemolytic-uremic syndrome, Tularemia, Peptic ulcer, Gastric and Duodenal ulcers, Legionnaire's Disease, Pontiac fever, Leptospirosis, Listeriosis, Leprosy (Hansen's disease), Tuberculosis, Gonorrhea, Ophthalmia neonatorum, Septic arthritis, Meningococcal disease including meningitis, Waterhouse-Friderichsen syndrome, *Pseudomonas* infection, Rocky mountain spotted fever, Typhoid fever type salmonellosis, Salmonellosis with gastroenteritis and enterocolitis, Bacillary dysentery/Shigellosis, Coagulase-positive

staphylococcal infections: Localized skin infections including Diffuse skin infection (Impetigo), Deep localized infections, Acute infective endocarditis, Septicemia, Necrotizing pneumonia, Toxinoses such as Toxic shock syndrome and Staphylococcal food poisoning, Cystitis, Endometritis, Otitis media, Streptococcal pharyngitis, Scarlet fever, Rheumatic fever, Puerperal fever, Necrotizing fasciitis, Cholera, Plague (including Bubonic plague and Pneumonic plague), as well as any infection caused by a bacteria selected from but not limited to *Helicobacter pylori*, *Borrelia burgdorferi*, *Legionella pneumophila*, *Mycobacteria* sps (e.g., *M. tuberculosis*, *M. avium*, *M. Intracellulare*, *M. kansasii*, *M. goodii*), *Staphylococcus aureus*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Listeria monocytogenes*, *Streptococcus pyogenes* (Group A *Streptococcus*), *Streptococcus agalactiae* (Group B *Streptococcus*), *Streptococcus* (viridans group), *Streptococcus faecalis*, *Streptococcus bovis*, *Streptococcus* (anaerobic sps.), *Streptococcus pneumoniae*, pathogenic *Campylobacter* sp., *Enterococcus* sp., *Haemophilus influenzae*, *Bacillus anthracis*, *Corynebacterium diphtheriae*, *Corynebacterium* sp., *Erysipelothrix rhusiopathiae*, *Clostridium perfringens*, *Clostridium tetani*, *Enterobacter erogenes*, *Klebsiella pneumoniae*, *Pasteurella multocida*, *Bacteroides* sp., *Fusobacterium nucleatum*, *Sreptobacillus moniliformis*, *Treponema pallidum*, *Treponema pertenue*, *Leptospira*, and *Actinomyces israelii*.

Non limiting examples of infectious disorder and/or disease caused by virus is selected from the group consisting of but not limited to acquired immune deficiency (AIDS), West Nile encephalitis, coronavirus infection, rhinovirus infection, influenza, dengue, hemorrhagic fever; an otological infection; severe acute respiratory syndrome (SARS), acute febrile pharyngitis, pharyngoconjunctival fever, epidemic keratoconjunctivitis, infantile gastroenteritis, infectious mononucleosis, Burkitt lymphoma, acute hepatitis, chronic hepatitis, hepatic cirrhosis, hepatocellular carcinoma, primary HSV-1 infection, (gingivostomatitis in children, tonsillitis & pharyngitis in adults, keratoconjunctivitis), latent HSV-1 infection (herpes labialis, cold sores), aseptic meningitis, Cytomegalovirus infection, Cytomegalic inclusion disease, Kaposi sarcoma, Castleman disease, primary effusion lymphoma, influenza, measles, encephalitis, postinfectious encephalomyelitis, Mumps, hyperplastic epithelial lesions (common, flat, plantar and anogenital warts, laryngeal papillomas, epidermodysplasia verruciformis), croup, pneumonia, bronchiolitis, Poliomyelitis, Rabies, bronchiolitis, pneumonia, German measles, congenital rubella, Hemorrhagic Fever, Chickenpox, Dengue, Ebola infection, Echovirus infection, EBV infection, Fifth Disease, Filovirus, Flavivirus, Hand, foot & mouth disease, Herpes Zoster Virus (Shingles), Human Papilloma Virus Associated Epidermal Lesions, Lassa Fever, Lymphocytic choriomeningitis, Parainfluenza Virus Infection, Paramyxovirus, Parvovirus B 19 Infection, Picornavirus, Poxviruses infection, Rotavirus diarrhea, Rubella, Rubella, Varicella, Variola infection.

An infectious disorder and/or disease caused by fungi optionally includes but is not limited to Allergic bronchopulmonary aspergillosis, Aspergilloma, Aspergillosis, Basidiobolomycosis, Blastomycosis, Candidiasis, Chronic pulmonary aspergillosis, Chytridiomycosis, Coccidioidomycosis, Conidiobolomycosis, Covered smut (barley), Cryptococcosis, Dermatophyte, Dermatophytid, Dermatophytosis, Endothrix, Entomopathogenic fungus, Epizootic lymphangitis, Epizootic ulcerative syndrome, Esophageal candidiasis, Exothrix, Fungemia, Histoplasmosis, Lobomycosis, Massospora cicadina, Mycosis, Mycosphaerella fragariae, Myringomycosis, Paracoccidioidomycosis, Pathogenic fungi, Penicillio-

sis, Thousand cankers disease, Tinea, Zeaspora, Zygomycosis. Non limiting examples of infectious disorder and/or disease caused by parasites is selected from the group consisting of but not limited to Acanthamoeba, Amoebiasis, Ascariasis, Ancylostomiasis, Anisakiasis, Babesiosis, Balantidiasis, Baylisascariasis, Blastocystosis, Candiru, Chagas disease, Clonorchiasis, Cochliomyia, Coccidia, Chinese Liver Fluke Cryptosporidiosis, Dientamoebiasis, Diphylobothriasis, Dioctophyme renalis infection, Dracunculiasis, Echinococcosis, Elephantiasis, Enterobiasis, Fascioliasis, Fasciolopsiasis, Filariasis, Giardiasis, Gnathostomiasis, Hymenolepiasis, Halzoun Syndrome, Isosporiasis, Katayama fever, Leishmaniasis, lymphatic filariasis, Malaria, Metagonimiasis, Myiasis, Onchocerciasis, Pediculosis, Primary amoebic meningoencephalitis, Parasitic pneumonia, Paragonimiasis, Scabies, Schistosomiasis, Sleeping sickness, Strongyloidiasis, Sparganosis, Rhinosporidiosis, River blindness, Taeniasis (cause of Cysticercosis), Toxocariasis, Toxoplasmosis, Trichinosis, Trichomoniasis, Trichuriasis, Trypanosomiasis, Tapeworm infection.

A preferred example of infectious disease is a disease caused by any of hepatitis B, hepatitis C, infectious mononucleosis, EBV, cytomegalovirus, AIDS, HIV-1, HIV-2, tuberculosis, malaria and schistosomiasis.

As used herein, the term "vaccine" refers to a biological preparation that improves immunity to a particular disease, wherein the vaccine includes an antigen, such as weakened or killed forms of pathogen, its toxins or one of its surface proteins, against which immune responses are elicited. A vaccine typically includes an adjuvant as immune potentiator to stimulate the immune system. As used herein, the term "therapeutic vaccine" and/or "therapeutic vaccination" refers to a vaccine used to treat ongoing disease, such as infectious disease or cancer.

As used herein, the term "adjuvant" refers to an agent used to stimulate the immune system and increase the response to a vaccine, without having any specific antigenic effect in itself.

As used herein, the term LY6G6F and/or LY6G6F protein(s) refers to any one of the proteins set forth in SEQ ID NO:1, and/or variants thereof, and/or orthologs and/or fragments thereof, and/or nucleic acid sequences encoding for same, that are differentially expressed in cancers as recited herein and/or in infectious disorders as recited herein, and/or immune related disorders as recited herein, and/or that play a role in the etiology of cancers, and/or in infectious disorders, and/or immune related disorders.

According to preferred embodiments, a LY6G6F fragment comprises an amino acid sequence of LY6G6F ectodomain, set forth in any one of SEQ ID NOs: 2, 59, 81, 96, and/or variants thereof. According to preferred embodiments, a LY6G6F ortholog comprises any one of SEQ ID NOs:20, 29. According to preferred embodiments, a nucleic acid sequence encoding LY6G6F protein comprises SEQ ID NO:33, 57 or 182.

As used herein, the term VSIG10 and/or VSIG10 protein(s) refers to any one of the proteins set forth in any one of SEQ ID NOs:3, 5, and/or variants thereof, and/or orthologs and/or fragments thereof, and/or nucleic acid sequences encoding for same, that are differentially expressed in cancers as recited herein and/or in infectious disorders as recited herein, and/or immune related disorders as recited herein, and/or that play a role in the etiology of cancers and/or in infectious disorders, and/or immune related disorders.

According to preferred embodiments, a VSIG10 fragment comprises an amino acid sequence of VSIG10 ectodomain, set forth in any one of SEQ ID NOs: 4, 6, 60, 61, 82-93,

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97-100, and/or variants thereof, and/or an amino acid sequence comprising a VSIG10 variant (SEQ ID NO:5) unique edge portion, demonstrated in FIG. 2A. According to preferred embodiments, a VSIG10 ortholog comprises any one of SEQ ID NOs: 19, 30. According to preferred embodiments, a nucleic acid sequence encoding VSIG10 protein comprises any one of SEQ ID NOs: 34, 35, 36, 183, or 184.

As used herein, the term TMEM25 and/or TMEM25 protein(s) refers to any one of the proteins set forth in any one of SEQ ID NOs: 7, 39, and/or variants thereof, and/or orthologs and/or fragments thereof, and/or nucleic acid sequences encoding for same, that are differentially expressed in cancers as recited herein and/or in infectious disorders as recited herein, and/or immune related disorders as recited herein, and/or that play a role in the etiology of cancers and/or in infectious disorders, and/or immune related disorders.

According to preferred embodiments, a TMEM25 fragment comprises an amino acid sequence of TMEM25 ectodomain, set forth in any one of SEQ ID NOs: 8, 39, 94, 101 and/or variants thereof. According to preferred embodiments, a TMEM25 ortholog comprises a protein having a sequence according to any of SEQ ID NO: 9, and/or 28. According to preferred embodiments, a nucleic acid sequence encoding TMEM25 protein comprises any one of SEQ ID NOs: 37 or 185.

As used herein, the term LSR and/or LSR protein(s) refers to any one of the proteins set forth in any one of SEQ ID NOs: 11, 13, 15-18, 143, and/or variants thereof, and/or orthologs and/or fragments thereof, and/or nucleic acid sequences encoding for same, that are differentially expressed in cancers as recited herein and/or in infectious disorders as recited herein, and/or immune related disorders as recited herein, and/or that play a role in the etiology of cancers and/or in infectious disorders, and/or immune related disorders.

According to preferred embodiments, a LSR fragment comprises an amino acid sequence of LSR ectodomain, set forth in any one of SEQ ID NOs: 10, 12, 14, 22, 47-50, 95, 102, and/or variants thereof, and/or an amino acid sequence comprising a LSR variant (SEQ ID NO:18) unique edge portion, demonstrated in FIG. 2G. An example of LSR orthologs is presented in any one of SEQ ID NOs: 21, 31, 32. According to preferred embodiments, a nucleic acid sequence encoding LSR protein comprises any one of SEQ ID NOs: 40-46, 132, 155, 188, 186, 187, 145, 154.

Without wishing to be limited by a single hypothesis, each of the LY6G6F, VSIG10, TMEM25 and/or LSR proteins according to at least some embodiments of the present invention, was predicted to be an immune costimulatory protein, e.g., a B7 protein family member that is involved in B7 immune co-stimulation including for example T cell responses elicited against cancer cells and that elicit effects on immunity such as triggering of autoimmune effects.

As used herein, the term the "soluble ectodomain (ECD)" or "ectodomain" or "soluble LY6G6F, VSIG10, TMEM25 and/or LSR protein(s)/molecule(s)" of LY6G6F, VSIG10, TMEM25 and/or LSR means non-cell-surface-bound (i.e.

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circulating) LY6G6F, VSIG10, TMEM25 and/or LSR molecules or any portion thereof, including, but not limited to: LY6G6F, VSIG10, TMEM25 and/or LSR-Ig fusion proteins, wherein the extracellular domain of LY6G6F, VSIG10, TMEM25 and/or LSR is fused to an immunoglobulin (Ig) moiety rendering the fusion molecule soluble, or fragments and derivatives thereof, proteins with the extracellular domain of LY6G6F, VSIG10, TMEM25 and/or LSR fused or joined with a portion of a biologically active or chemically active protein such as the papillomavirus E7 gene product, melanoma-associated antigen p97 or HIV env protein, or fragments and derivatives thereof; hybrid (chimeric) fusion proteins such as LY6G6F, VSIG10, TMEM25 and/or LSR-Ig, or fragments and derivatives thereof. Such fusion proteins are described in greater detail below.

"Soluble LY6G6F, VSIG10, TMEM25 and/or LSR protein(s)/molecule(s)" also include LY6G6F, VSIG10, TMEM25 and/or LSR molecules with the transmembrane domain removed to render the protein soluble, or fragments and derivatives thereof; fragments, portions or derivatives thereof, and soluble LY6G6F, VSIG10, TMEM25 and/or LSR mutant molecules. The soluble LY6G6F, VSIG10, TMEM25 and/or LSR molecules used in the methods according to at least some embodiments of the invention may or may not include a signal (leader) peptide sequence.

Fragments of LY6G6F Polypeptides

The term the "soluble ectodomain (ECD)" or "ectodomain" or "soluble" form of LY6G6F refers also to the nucleic acid sequences encoding the corresponding proteins of LY6G6F "soluble ectodomain (ECD)" or "ectodomain" or "soluble LY6G6F proteins/molecules"). Optionally, the LY6G6F ECD refers to any one of the polypeptide sequences below and/or listed in Table A below, and/or fragments or variants thereof possessing at least 80% sequence identity, more preferably at least 90% sequence identity therewith and even more preferably at least 95, 96, 97, 98 or 99% sequence identity therewith, and/or conjugates thereof, and/or polynucleotides encoding same:

SEQ ID NO: 2, amino acid residues 17-234 (not including signal peptide, up till transmembrane) (FIG. 1A):
ADNMQAIYVALGEAVELPCPSPTTLHGDEHLSWFCSPAAGSFTTLVAQV
QVGRPADDPGKPGRESRLRLGNYSWLWEGSKEEDAGRYWCAVLGQHNN
YQNRVRYDVLVKGSQLSARAADGSPCNVLLCSVVPSSRRMDSVTWQEGK
GPVRGRVQSPFWGSEAAALLVCPGEGLESEPRRRPRIIRCLMTHNKGVSF
SLAASIDASPALCAPSTGWDMP,

and fragments and variants thereof possessing at least 80% sequence identity, more preferably at least 90% sequence identity therewith and even more preferably at least 95, 96, 97, 98 or 99% sequence identity therewith. SEQ ID NO:59 represents an example of the LY6G6F ECD including signal peptide.

TABLE A

SEQ ID NO: Amino acid sequence	Description
81 ADNMQAIYVALGEAVELPCPSPTTLHGDEHLSWFCSPAAGSFTTLVAQVQVGRPADDPGKPGRESRLRLGNYSWLWEGSKEEDAGRYWCAVLGQHNNYQNRVRYD	LY6G6F_IgV_domain aa 17-122 of seq id: 1

Optionally, the fragment is of at least about 62, 63, 64, 65 and so forth amino acids of the extracellular domain of LY6G6F protein, set forth in SEQ ID NO: 1, up to 228 amino acids of the LY6G6F protein extracellular domain, optionally including any integral value between 62 and 228 amino acids in length. Preferably, the fragment is of at least about 62 and up to 82 amino acids of the LY6G6F protein extracellular domain, optionally including any integral value between 62 and 82 amino acids in length. Also preferably the fragment is of at least about 95 up to 115 amino acids of the LY6G6F protein extracellular domain, optionally including any integral value between 95 and 115 amino acids in length. Also preferably the fragment is of at least about 208 up to 228 amino acids of the LY6G6F protein extracellular domain, optionally including any integral value between 208 and 228 amino acids in length. More preferably, the fragment is about 72 or 106 or 218 amino acids. The LY6G6F fragment protein according to at least some embodiments of the invention may or may not include a signal peptide sequence, and may or may not include 1, 2, 3, 4, or 5 contiguous amino acids from the LY6G6F transmembrane domain.

In particular, the fragments of the extracellular domain of LY6G6F can include any sequence corresponding to any portion of or comprising the IgV domain of the extracellular domain of LY6G6F, having any sequence corresponding to residues of LY6G6F (SEQ ID NO:1) starting from any position between 14 and 27 and ending at any position between 112 and 132.

The LY6G6F proteins contain an immunoglobulin domain within the extracellular domain, the IgV domain (or V domain), shown in FIG. 1 A in a box, which is related to the variable domain of antibodies. The IgV domain may be responsible for receptor binding, by analogy to the other B7 family members. The Ig domain of the extracellular domain includes one disulfide bond formed between intradomain cysteine residues, as is typical for this fold and may be important for structure-function. In SEQ ID NO: 1 these cysteines are located at residues 35 and 106.

In one embodiment, there is provided a soluble fragment of LY6G6F; as described in greater detail below with regard to the section on fusion proteins, such a soluble fragment may optionally be described as a first fusion partner. Useful fragments are those that retain the ability to bind to their natural receptor or receptors and/or retain the ability to inhibit T cell activation. A LY6G6F polypeptide that is a fragment of full-length LY6G6F typically has at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 98 percent, 99 percent, 100 percent, or even more than 100 percent of the ability to bind its natural receptor(s) and/or of the ability to inhibit T cell activation as compared to full-length LY6G6F. Soluble LY6G6F polypeptide fragments are fragments of LY6G6F polypeptides that may be shed, secreted or otherwise extracted from the producing cells. In other embodiments, the soluble fragments of LY6G6F polypeptides include fragments of the LY6G6F extracellular domain that retain LY6G6F biological activity, such as fragments that retain the ability to bind to their natural receptor or receptors and/or retain the ability to inhibit T cell activation. The extracellular domain can include 1, 2, 3, 4, or 5 contiguous amino acids from the transmembrane domain, and/or 1, 2, 3, 4, or 5 contiguous amino acids from the signal sequence. Alternatively, the extracellular domain can have 1, 2, 3, 4, 5 or more amino acids removed from the C-terminus, N-terminus, or both.

In some embodiments the LY6G6F extracellular domain polypeptide comprises the amino acid sequence of the IgV domain as set forth in any one of SEQ ID NO: 81, or frag-

ments or variants thereof, or the region between the conserved cysteines of the IgV domain located at residues 35 and 106 of the full-length protein SEQ ID NO:1, corresponding to the sequence set forth in SEQ ID NO: 96: CPSPTLHGDE-HLSWFCSPAAGSFTTLVAQVQVGRPAD-PGKPGRESRLRLGNY SLWLEGSKEEDAGRYWC. In other embodiments the LY6G6F extracellular domain polypeptide consists essentially of the amino acid sequence of the IgV domain as set forth in any one of SEQ ID NOs: 81 and 96.

Generally, the LY6G6F polypeptide fragments are expressed from nucleic acids that include sequences that encode a signal sequence. The signal sequence is generally cleaved from the immature polypeptide to produce the mature polypeptide lacking the signal sequence. The signal sequence of LY6G6F can be replaced by the signal sequence of another polypeptide using standard molecule biology techniques to affect the expression levels, secretion, solubility, or other property of the polypeptide. The signal peptide sequence that is used to replace the LY6G6F signal peptide sequence can be any known in the art.

Optionally, the LY6G6F ECD refers to any one of the nucleic acid sequences encoding LY6G6F ECD polypeptides, optionally to the nucleic acid sequences set forth in SEQ ID NO:33, or fragments thereof and/or degenerative variants thereof, encoding LY6G6F ECD polypeptides set forth in SEQ ID NO:2.

Optionally, the LY6G6F ECD refers to orthologous ECD polypeptides. Optionally, the LY6G6F ECD refers to mouse LY6G6F ECD polypeptides, set forth in SEQ ID NOs:20, and/or a mouse LY6G6F ECD-IgG2a-Fc-fused polypeptide, set forth in SEQ ID NOs:23.

Fragments of VSIG10 Polypeptides

The term the "soluble ectodomain (ECD)" or "ectodomain" or "soluble" form of VSIG10 refers also to the nucleic acid sequences encoding the corresponding proteins of VSIG10 "soluble ectodomain (ECD)" or "ectodomain" or "soluble VSIG10 proteins/molecules". Optionally, the VSIG10 ECD refers to any one of the polypeptide sequences below and/or listed in Table B below, and/or fragments or variants thereof possessing at least 80% sequence identity, more preferably at least 90% sequence identity therewith and even more preferably at least 95, 96, 97, 98 or 99% sequence identity therewith, and/or conjugates thereof, and/or polynucleotides encoding same:

SEQ ID NO: 4, amino acid residues 31-413 (not including signal peptide, up till transmembrane) (FIG. 1B):
 VVIGEVHENVTLHCGNISGLRGQVTWYRNNSPEVFLSSNSSLRPAEPR
 FSLVDATSLHIESLSLGDGIYTCQEILNVTQWFQVWLQVAGSPYQIEV
 HIVATGTLPNGTLYAARGSQVDFSCNSSSRPPVVEWFQALNSSSESF
 GHNLTVNFFSLLLISPQLQGNITCLALNQLSKRHRKVTTELLVYPPPS
 APQCWAQMASGSFMLQLTCRWDGGYPDPDFLWIEEPGGVIVGSKLQVE
 MLSESQLSDGKKFKCVTSHIVGPESGASCMVQIRGPSLLSEPMKTCFTG
 GNVTLTCQVSGAYPPAKILWLRNLTPQEVIIQPSRHLITQDQGNSTLT
 IHNCSDLDDEGYICRADSPVGVREMEIWSVKEPLNIGG;

-continued

SEQ ID NO: 6, amino acid residues 31-312 (skipping exon 3 variant, not including signal peptide, up till transmembrane) (FIG. 1C):
VVIGEVHENVTLHCGNISGLRGQVTWYRNNSEPVFLSSNSSLRPAEPR

FSLVDATSLHIESLSLGDEGIYTCQEILNVTQWFQVWLQVANPPPSAPQ

CWAQMASGSFMLQLTCRWDGGYDPDFLWIEEPGGVIVGKSKLGVEMLS

ESQLSDGKKFKCVTSHIVGPESGASCMVQIRGPSLLSEPMKTCFTGGNV

-continued

TLTCQVSGAYPPAKILWLRNLTQPEVIIQPSSRHLITQDQGNSTLTIHN

5 CSQDLDEGYIICRADSPVGVREMEIWL SVKEPLNIGG,

and variants thereof possessing at least 80% sequence identity, more preferably at least 90% sequence identity therewith and even more preferably at least 95, 96, 97, 98 or 99% sequence identity therewith. SEQ ID NOs:60-61 represent examples of the VSIG10 ECD including signal peptide.

TABLE B

SEQ ID NO: Amino acid sequence	Description
82 VVIGEVHENVTLHCGNISGLRGQVTWYRNNSEPVFLSSNSSLRPAEPRFSLVDATSLHIESLSLGDEGIYTCQEILNVTQWFQVWLQV	VSIG10_IgC2_domain_1 aa 31-119 of seq id:3 aa 31-119 of seq id: 5
83 PYQIEVHIVATGTLPNGTLYAARGSQVDFSCNSSRPPPVVEWVFQALNSSSESFGHNLTVNFFSLLLISPNLQGNYTCLALNQLSKRHRKVT	VSIG10_IgC2_domain_2 aa 123-215 of seq id: 3
84 PPPSAPQCWAQMASGSFMLQLTCRWDGGYDPDFLWIEEPGGVIVGKSKLGVEMLSEQLSDGKKFKCVTSHIVGPESGASCMVQIR	VSIG10_IgC2_domain_3 aa 223-309 of seq id: 3 aa 122-208 of seq id: 5
85 PSLLEPMKTCFTGGNVTLTCQVSGAYPPAKILWLRNLTQPEVIIQPSSRHLITQDQGNSTLTIHNCSQDLDEGYIICRADSPVGVREMEIWL	VSIG10_IgC2_domain_4 aa 311-404 of seq id:3 aa 210-303 of seq id:5
86 VVIGEVHENVTLHCGNISGLRGQVTWYRNNSEPVFLSSNSSLRPAEPRFSLVDATSLHIESLSLGDEGIYTCQEILNVTQWFQVWLQVASGPYQIEVHIVATGTLPNGTLYAARGSQVDFSCNSSSRPPPVVEWVFQALNSSSESFGHNLTVNFFSLLLISPNLQGNYTCLALNQLSKRHRKVT	VSIG10_WT_IgC2_domains_1-2 aa 31-215 of seq id: 3
87 VVIGEVHENVTLHCGNISGLRGQVTWYRNNSEPVFLSSNSSLRPAEPRFSLVDATSLHIESLSLGDEGIYTCQEILNVTQWFQVWLQVASGPYQIEVHIVATGTLPNGTLYAARGSQVDFSCNSSSRPPPVVEWVFQALNSSSESFGHNLTVNFFSLLLISPNLQGNYTCLALNQLSKRHRKVTTELLVYPPPSAPQCWAQMASGSFMLQLTCRWDGGYDPDFLWIEEPGGVIVGKSKLGVEMLSEQLSDGKKFKCVTSHIVGPESGASCMVQIR	VSIG10_WT_IgC2_domains_1-3 aa 31-309 of seq id: 3
88 VVIGEVHENVTLHCGNISGLRGQVTWYRNNSEPVFLSSNSSLRPAEPRFSLVDATSLHIESLSLGDEGIYTCQEILNVTQWFQVWLQVASGPYQIEVHIVATGTLPNGTLYAARGSQVDFSCNSSSRPPPVVEWVFQALNSSSESFGHNLTVNFFSLLLISPNLQGNYTCLALNQLSKRHRKVTTELLVYPPPSAPQCWAQMASGSFMLQLTCRWDGGYDPDFLWIEEPGGVIVGKSKLGVEMLSEQLSDGKKFKCVTSHIVGPESGASCMVQIRGPSLLSEPMKTCFTGGNVTLTCQVSGAYPPAKILWLRNLTQPEVIIQPSSRHLITQDQGNSTLTIHNCSQDLDEGYIICRADSPVGVREMEIWL	VSIG10_WT_IgC2_domains_1-4 aa 31-404 of seq id: 3
89 PYQIEVHIVATGTLPNGTLYAARGSQVDFSCNSSRPPPVVEWVFQALNSSSESFGHNLTVNFFSLLLISPNLQGNYTCLALNQLSKRHRKVTTELLVYPPPSAPQCWAQMASGSFMLQLTCRWDGGYDPDFLWIEEPGGVIVGKSKLGVEMLSEQLSDGKKFKCVTSHIVGPESGASCMVQIR	VSIG10_WT_IgC2_domains_2-3 aa 123-309 of seq id: 3
90 PYQIEVHIVATGTLPNGTLYAARGSQVDFSCNSSRPPPVVEWVFQALNSSSESFGHNLTVNFFSLLLISPNLQGNYTCLALNQLSKRHRKVTTELLVYPPPSAPQCWAQMASGSFMLQLTCRWDGGYDPDFLWIEEPGGVIVGKSKLGVEMLSEQLSDGKKFKCVTSHIVGPESGASCMVQIRGPSLLSEPMKTCFTGGNVTLTCQVSGAYPPAKILWLRNLTQPEV	VSIG10_WT_IgC2_domains_2-4 aa 123-404 of seq id: 3

TABLE B -continued

SEQ ID NO: Amino acid sequence	Description
IIQPSSRHLITQDQGNSTLTIHNCSQDLDEGYI ICRADSPVGVREMEIWL	
91 PPPSAPQCWAQMASGSFMLQLTCRWGGYDPDP FLWIEEPGGVIVGKSKLGVEMLSQSLDGKKF KCVTSHIVGPESGASCMVQIRGPSLLSEPMKTC FTGGNVTLTCQVSGAYPPAKILWLRNLTQPEVI IQPSSRHLITQDQGNSTLTIHNCSQDLDEGYI CRADSPVGVREMEIWL	VSIG10_IgC2_domains_3-4 aa 223-404 of seq id: 3 aa 122-303 of seq id: 5
92 VVIGEVHENVTLHCGNISGLRGQVTWYRNNSEP VFLSSNSSLRPAEPRFSLVDATSLHI ESLSLGDEGIYTCQEILNVTQWFQVWLQVANPP PSAPQCWAQMASGSFMLQLTCRWGGY PDPDFLWIEEPGGVIVGKSKLGVEMLSQSLSD GKKFKCVTSHIVGPESGASCMVQIR	VSIG10_Variant_skipping_ exon_3_T95617_P6_IgC2_ domains_1,3 aa 31-208 of seq id: 5
93 VVIGEVHENVTLHCGNISGLRGQVTWYRNNSEP VFLSSNSSLRPAEPRFSLVDATSLHI ESLSLGDEGIYTCQEILNVTQWFQVWLQVANPP PSAPQCWAQMASGSFMLQLTCRWGGY PDPDFLWIEEPGGVIVGKSKLGVEMLSQSLSD GKKFKCVTSHIVGPESGASCMVQIRGP SLLSEPMKTCFTGGNVTLTCQVSGAYPPAKILW LRNLTQPEVI IQPSSRHLITQDQGNST LTIHNCSQDLDEGYI CRADSPVGVREMEIWL	VSIG10_Variant_skipping_ exon_3_T95617_P6_IgC2_ domains_1,3-4 aa 31-303 of seq id: 5

Optionally, the fragment is of at least about 36, 37, 38, 39, 40, 41, 42, 43, and so forth amino acids of the extracellular domain of VSIG10 protein, set forth in SEQ ID NO:3, up to 393 amino acids of the VSIG10 protein extracellular domain, optionally, including any integral value between 36 and 393 amino acids in length. Preferably, the fragment is of at least about 36 up to 70 amino acids of the VSIG10 protein extracellular domain, optionally including any integral value between 36 and 70 amino acids in length. Also preferably the fragment is of at least about 80 up to 100 amino acids of the VSIG10 protein extracellular domain, optionally including any integral value between 80 and 100 amino acids in length. Also preferably the fragment is of at least about 170 up to 200 amino acids of the VSIG10 protein extracellular domain, optionally including any integral value between 170 and 200 amino acids in length. Also preferably the fragment is of at least about 265 up to 290 amino acids of the VSIG10 protein extracellular domain, optionally including any integral value between 265 and 290 amino acids in length. Also preferably the fragment is of at least about 365 up to 393 amino acids of the VSIG10 protein extracellular domain, optionally including any integral value between 365 and 393 amino acids in length. More preferably, the fragment is about 46, 49, 58, 60, 87, 89, 93, 94, 178, 182, 185, 187, 273, 279, 282, 374, 383 amino acids. The VSIG10 fragment protein according to at least some embodiments of the invention may or may not include a signal peptide sequence, and may or may not include 1, 2, 3, 4, or 5 contiguous amino acids from the VSIG10 transmembrane domain.

In particular, the fragments of the extracellular domain of VSIG10 can include any sequence corresponding to any portion of or comprising of one or more of the IgC2 domains of the extracellular domain of VSIG10, having any sequence corresponding to residues of VSIG10 (SEQ ID NO:3) starting from any position between 28 and 41 and ending at any position between 109 and 122 or starting from any position between 120 and 133 and ending at any position between 205 and 222 or starting from any position between 216 and 233

and ending at any position between 299 and 310 or starting from any position between 310 and 321 and ending at any position between 394 and 414 or starting from any position between 28 and 41 and ending at any position between 205 and 222 or starting from any position between 28 and 41 and ending at any position between 299 and 310 or starting from any position between 28 and 41 and ending at any position between 394 and 414 or starting from any position between 120 and 133 and ending at any position between 299 and 310 or starting from any position between 120 and 133 and ending at any position between 394 and 414 or starting from any position between 216 and 233 and ending at any position between 394 and 414, or having any sequence corresponding to residues of VSIG10_Variant_skipping_exon_3_T95617_P6 (SEQ ID NO:5) starting from any position between 28 and 41 and ending at any position between 198 and 209 or starting from any position between 28 and 41 and ending at any position between 293 and 313.

The VSIG10 proteins contain immunoglobulin domains within the extracellular domain, IgC2 domain (or Ig-like C2 domain or Ig C2-set domain), which is related to the constant domain of antibodies. The domains are illustrated in FIG. 1B (for SEQ ID NO:3) and in FIG. 1C (for SEQ ID NO:5). The Ig domains of the extracellular domain include one disulfide bond formed between intradomain cystein residues, as is typical for this fold and may be important for structure-function. In SEQ ID NO: 3 these cysteines are located at residues 44 and 103 and at residues 153 and 201 and at residues 245 and 290 and at residues 331 and 388. In SEQ ID NO:5 these cysteines are located at residues 44 and 103 and 144 and 189 and at residues 230 and 287.

In one embodiment, there is provided a soluble fragment of VSIG10, which may optionally be described as a first fusion partner in the below section on fusion proteins. Useful fragments are those that retain the ability to bind to their natural receptor or receptors and/or retain the ability to inhibit T cell activation. A VSIG10 polypeptide that is a fragment of full-

length VSIG10 typically has at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 98 percent, 99 percent, 100 percent, or even more than 100 percent of the ability to bind its natural receptor(s) and/or of the ability to inhibit T cell activation as compared to full-length VSIG10. Soluble VSIG10 polypeptide fragments are fragments of VSIG10 polypeptides that may be shed, secreted or otherwise extracted from the producing cells. In other embodiments, the soluble fragments of VSIG10 polypeptides include fragments of the VSIG10 extracellular domain that retain VSIG10 biological activity, such as fragments that retain the ability to bind to their natural receptor or receptors and/or retain the ability to inhibit T cell activation. The extracellular domain can include 1, 2, 3, 4, or 5 contiguous amino acids from the transmembrane domain, and/or 1, 2, 3, 4, or 5 contiguous amino acids from the signal sequence. Alternatively, the extracellular domain can have 1, 2, 3, 4, 5 or more amino acids removed from the C-terminus, N-terminus, or both.

In some embodiments the VSIG10 extracellular domain polypeptide comprises the amino acid sequence of at least one of the IgC2 domains as set forth in any one of SEQ IDS NO: 82, 83, 84 and 85, or fragments or variants thereof, or the regions between the conserved cysteines of the IgC2 domains located at residues 44 and 103 of the full-length protein SEQ ID NO:3, corresponding to the sequence set forth in SEQ ID NO: 97: CGNISGLRGQVTWYRNNSEPVFLSSNS-SLRPAEPRFSLVDATSLHIESLSLGDEGI YTC, or located at residues 153 and 201 of the full-length protein SEQ ID NO:3, corresponding to the sequence set forth in SEQ ID NO: 98: CNSSSRPPPVVEWWFQALNSSSESF-GHNLTVNFFSLLISPQLGNYTC or located at residues 245 and 209 of the full-length protein SEQ ID NO:3, corresponding to the sequence set forth in SEQ ID NO: 99: CRWDGGYPDPDFLWIEEPGGVIVGK-SKLGVEMLSESQSLSDGKKFKC or located at residues 331 and 388 of the full-length protein SEQ ID NO:3, corresponding to the sequence set forth in SEQ ID NO: 100: CQVSGAY-PPAKILWLRNLTQPEVIIQPSSRHL-ITQDGQNSTLTIHNCSDQLDEGYI C. In some further

optionally to the nucleic acid sequences set forth in SEQ ID NOs:34, 36, or fragments thereof and/or degenerative variants thereof, encoding VSIG10 ECD polypeptides set forth in SEQ ID NOs:4, 6, respectively.

Optionally, the VSIG10 ECD refers to orthologous ECD polypeptides. Optionally, the VSIG10 ECD refers to mouse VSIG10 ECD polypeptides, set forth in SEQ ID NO:19, and/or a mouse VSIG10 ECD-IgG2a-Fc-fused polypeptide, set forth in SEQ ID NO:24.

Fragments of TMEM25 Polypeptides

The term the "soluble ectodomain (ECD)" or "ectodomain" or "soluble" form of TMEM25 refers also to the nucleic acid sequences encoding the corresponding proteins of TMEM25 "soluble ectodomain (ECD)" or "ectodomain" or "soluble TMEM25 proteins/molecules". Optionally, the TMEM25 ECD refers to any one of the polypeptide sequences below and/or listed in Table C below, and/or fragments or variants thereof possessing at least 80% sequence identity, more preferably at least 90% sequence identity therewith and even more preferably at least 95, 96, 97, 98 or 99% sequence identity therewith, and/or conjugates thereof, and/or polynucleotides encoding same:

SEQ ID NO: 8, amino acid residues 27-232 (not including signal peptide, up till transmembrane) (FIG. 1D):
 ELEPQIDGQTTWAERALRENERHAFTCRVAGGPGTPRLAWYLDGQLQEAS
 TSRLLSVVGGEAFSGGTSTFTVTAHRAQHELNCSLDPRSGRSANASVIL
 INVQFKPEIAQVGAKYQEAQGPGLLVLPALVRANPPANVTWIDQGPVT
 VNTSDFLVLDQNYFPWLTNHTVQLQLRSLAHNLSVVATNDVGVTASLSP
 APGLLATRVE,

and variants thereof possessing at least 80% sequence identity, more preferably at least 90% sequence identity therewith and even more preferably at least 95, 96, 97, 98 or 99% sequence identity therewith. SEQ ID NO:39 represents example of the TMEM25 ECD including signal peptide.

TABLE C

SEQ ID NO:	Amino acid sequence	Description
94	PQIDGQTTWAERALRENERHAFTCRVAGGPGTPRLAWYLDGQLQEASTSRLLSVVGGEAFSGGTSTFTVTAHRAQHELNCSLDPRSGRSANASVIL	TMEM25-IgC2_domain aa 30-123 of seq id: 7

embodiments the VSIG10 extracellular domain polypeptide consists essentially of amino acid sequence of at least one of SEQ IDS NOs: 82-93, 97-100.

Generally, the VSIG10 polypeptide fragments are expressed from nucleic acids that include sequences that encode a signal sequence. The signal sequence is generally cleaved from the immature polypeptide to produce the mature polypeptide lacking the signal sequence. The signal sequence of VSIG10 can be replaced by the signal sequence of another polypeptide using standard molecule biology techniques to affect the expression levels, secretion, solubility, or other property of the polypeptide. The signal peptide sequence that is used to replace the VSIG10 signal peptide sequence can be any known in the art.

Optionally, the VSIG10 ECD refers also to any one of the nucleic acid sequences encoding VSIG10 ECD polypeptides,

Optionally, the fragment is of at least about 46, 47, 48, 49, 50, 51, 52, and so forth amino acids of the extracellular domain of TMEM25 protein, set forth in SEQ ID NO:7, up to 216 amino acids of the TMEM25 protein extracellular domain, optionally including any integral value between 46 and 216 amino acids in length. Preferably, the fragment is of at least about 46 up to 66 amino acids of the TMEM25 protein extracellular domain, optionally including any integral value between 46 and 66 amino acids in length. Also preferably the fragment is of at least about 84 up to 104 amino acids of the TMEM25 protein extracellular domain, optionally including any integral value between 84 and 104 amino acids in length. Also preferably the fragment is of at least about 196 up to 216 amino acids of the TMEM25 protein extracellular domain, optionally including any integral value between 196 and 216 amino acids in length. More preferably, the fragment is about

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56 or 94 or 206 amino acids. The TMEM25 fragment protein according to at least some embodiments of the invention may or may not include a signal peptide sequence, and may or may not include 1, 2, 3, 4, or 5 contiguous amino acids from the TMEM25 transmembrane domain.

In particular, the fragments of the extracellular domain of TMEM25 can include any sequence corresponding to any portion of or comprising the IgC2 domain of the extracellular domain of TMEM25, having any sequence corresponding to residues of TMEM25 (SEQ ID NO:7) starting from any position between 27 and 40 and ending at any position between 113 and 133.

The TMEM25 proteins contain an immunoglobulin domain within the extracellular domain, IgC2 domain (or Ig-like C2 domain or Ig C2-set domain), which is related to the constant domain of antibodies. The domain is shown in FIG. 1D in a box. The Ig domain of the extracellular domain includes one disulfide bond formed between intradomain cysteine residues, as is typical for this fold and may be important for structure-function. In SEQ ID NO: 7 these cysteines are located at residues 52 and 107.

In one embodiment, there is provided a soluble fragment of TMEM25, which may optionally be described as a first fusion partner, as for example in the detailed section on fusion proteins below. Useful fragments are those that retain the ability to bind to their natural receptor or receptors and/or retain the ability to inhibit T cell activation. A TMEM25 polypeptide that is a fragment of full-length TMEM25 typically has at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 98 percent, 99 percent, 100 percent, or even more than 100 percent of the ability to bind its natural receptor(s) and/or of the ability to inhibit T cell activation as compared to full-length TMEM25. Soluble TMEM25 polypeptide fragments are fragments of TMEM25 polypeptides that may be shed, secreted or otherwise extracted from the producing cells. In other embodiments, the soluble fragments of TMEM25 polypeptides include fragments of the TMEM25 extracellular domain that retain TMEM25 biological activity, such as fragments that retain the ability to bind to their natural receptor or receptors and/or retain the ability to inhibit T cell activation. The extracellular domain can include 1, 2, 3, 4, or 5 contiguous amino acids from the transmembrane domain, and/or 1, 2, 3, 4, or 5 contiguous amino acids from the signal sequence. Alternatively, the extracellular domain can have 1, 2, 3, 4, 5 or more amino acids removed from the C-terminus, N-terminus, or both.

In some embodiments the TMEM25 extracellular domain polypeptide comprises the amino acid sequence of IgC2 domain, as set forth in any one of SEQ ID NO: 94, or fragments or variants thereof, or the region between the conserved cysteines of the IgC2 domain located at residues 52 and 107 of the full-length protein SEQ ID NO:7, corresponding to the sequence set forth in SEQ ID NO: 101: CRVAGGPGT-PRLAWYLDGQLQEASTSRLLSVGGGEAF-SGGTSTFTVTAHRAQHEL NC. In other embodiments the TMEM25 extracellular domain polypeptide consists essentially of the amino acid sequence of the IgC2 domain as set forth in any one of SEQ ID NOs: 94 and 101.

Generally, the TMEM25 polypeptide fragments are expressed from nucleic acids that include sequences that encode a signal sequence. The signal sequence is generally cleaved from the immature polypeptide to produce the mature polypeptide lacking the signal sequence. The signal sequence of TMEM25 can be replaced by the signal sequence of another polypeptide using standard molecule biology techniques to affect the expression levels, secretion, solubility, or

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other property of the polypeptide. The signal peptide sequence that is used to replace the TMEM25 signal peptide sequence can be any known in the art.

Optionally, the TMEM25 ECD refers also to any one of the nucleic acid sequences encoding TMEM25 ECD polypeptides, optionally to the nucleic acid sequences set forth in SEQ ID NO:37, or fragments thereof and/or degenerative variants thereof, encoding TMEM25 ECD polypeptides set forth in SEQ ID NO:8

Optionally, the TMEM25 ECD refers to orthologous ECD polypeptides. Optionally, the TMEM25 ECD refers to mouse TMEM25 ECD polypeptides, set forth in SEQ ID NOs:9, and/or a mouse TMEM25 ECD-IgG2a-Fc-fused polypeptide, set forth in SEQ ID NOs:25.

Fragments of LSR Polypeptides

The term the "soluble ectodomain (ECD)" or "ectodomain" or "soluble" form of LSR refers also to the nucleic acid sequences encoding the corresponding proteins of LSR "soluble ectodomain (ECD)" or "ectodomain" or "soluble LSR proteins/molecules". Optionally, the LSR ECD refers to any one of the polypeptide sequences below and/or listed in Table D below, and/or fragments or variants thereof possessing at least 80% sequence identity, more preferably at least 90% sequence identity therewith and even more preferably at least 95, 96, 97, 98 or 99% sequence identity therewith, and/or conjugates thereof, and/or polynucleotides encoding same:

SEQ ID NO: 12, LSR isoform A ECD (not including signal peptide, up till transmembrane) amino acid residues 42-211 (FIG. 1E):

```
IQVTVSNPYHVILFQPVTLPCITYQMTSTPTQPIVIWKYKSFCDRIAD
AFSPASVDNQLNAQLAAGNPGYNPYVEQCDSVRTVRVATKQGNVATLGL
DYYQGRRIITIGNADLTFDQTAWGDSGVYYCSVSAQDLQGNNEAYAE
IVLGRGTSVGAELLPGFQAGPIED;
```

SEQ ID NO: 14, LSR isoform B ECD (not including signal peptide, up till transmembrane) amino acid residues 42-192 (FIG. 1F):

```
IQVTVSNPYHVILFQPVTLPCITYQMTSTPTQPIVIWKYKSFCDRIAD
AFSPASVDNQLNAQLAAGNPGYNPYVEQCDSVRTVRVATKQGNVATLGL
DYYQGRRIITIGNADLTFDQTAWGDSGVYYCSVSAQDLQGNNEAYAE
IVLD;
```

SEQ ID NO: 47, LSR isoform C secreted variant amino acid residues 42-533 (FIG. 1G):

```
IQVTVSNPYHVILFQPVTLPCITYQMTSTPTQPIVIWKYKSFCDRIAD
AFSPASVDNQLNAQLAAGNPGYNPYVEQCDSVRTVRVATKQGNVATLGL
DYYQGRRIITIGNADLTFDQTAWGDSGVYYCSVSAQDLQGNNEAYAE
IVLVYAAGKAATSGVPSIYAPSTYAHLSPAKTPPPAMIPMGPAYNGYP
GGYPGDVDRSSSAGGQGSYVPLLRDTSVASEVRSYRIQASQDDSM
RVLYYMEKELANFDPSPRGPSSGRVERAMSEVTS LHEDDWRSRPSRGPA
LTPIRDEEWGGHSPRSPRGWDQEPAREQAGGGWRARRPRARSVDALDDL
TPPSTAESGSRSPSTNGGRSRAYMPPRSRSRDDLYQDDSRDFPRSRDP
HYDDFRSRERPPADPRSHHHRTRDPRDNGSRSGDLPYDGRLLLEAVRKK
GSEERRRPHKEEEEAYYPAPPYPYSETDSQASRERRLKKNLALSRESL
VV;
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-continued

SEQ ID NO: 48, LSR isoform D secreted variant
amino acid residues 42-532 (FIG. 1H)
IQVTVSNPYHVILFQPVTLPCYQMTSTPTQPIVIWKYSFCRDRIAD
AFSPASVDNQLNAQLAAGNPGYNPYVEQCDSVRTVRVVATKQGNVATLG
DYYQGRRITITGNADLTFDQTAWGDSGVYCSVVSAQDLQGNNEAYAE
IVLVYAAGKAATSGVPSIYAPSTYAHLSPAKTPPPAMIPMGPAYNGYP
GGYPGDVDRSSSAGGQGSYVPLLRDTSVASVRSYRIQASQQDDSMR
VLYYMEKELANFDPSPRGPPSGRVERAMSEVTS LHEDDWSRPSRGPAL
TPIRDEEWGGHSPRSPRGWDQEPAREQAGGWRARRPRARSVDALDDL
TPSTAESGSRSPSTNGGRSRAYMPPRSRSRDDLYQDDSRDFPFRSRDPH
YDDERSRERPPADPRSHHHRTRDPRDNGSRSGDLPYDGRLLLEEAVRKKG
SEERRRPKHEEEAYYPAPPYSETDSQASRERRLKKNLALSRESLV
V;
SEQ ID NO: 49, LSR isoform E secreted variant
amino acid residues 42-493 (FIG. 1I):
IQVTVSNPYHVILFQPVTLPCYQMTSTPTQPIVIWKYSFCRDRIAD
AFSPASVDNQLNAQLAAGNPGYNPYVEQCDSVRTVRVVATKQGNVATLG

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-continued

RDDLYDQDDSRDFPFRSRDPHYDDFRSRERPPADPRSHHHRTRDPRDNGS
RSGDLPYDGRLLLEEAVRKKGSEERRRPKHEEEAYYPAPPYSETDS
QASRERRLKKNLALSRESLV,
and variants thereof possessing at least 80% sequence iden-
tity, more preferably at least 90% sequence identity therewith
and even more preferably at least 95, 96, 97, 98 or 99%
sequence identity therewith. SEQ ID NOs:10, 22 represent
example of the LSR ECD including signal peptide.

Optionally, the fragment is of at least about 100, 101, 102,
103, 104, 105, 106, 107, 108, 109, 110 and so forth amino
acids of the extracellular domain of LSR protein, set forth in
SEQ ID NO:11 and/or 143, up to 198 amino acids of the
extracellular domain, optionally including any integral value
between 100 and 198 amino acids in length. The LSR frag-
ment protein according to at least some embodiments of the
invention may or may not include a signal peptide sequence,
and may or may not include 1, 2, 3, 4, or 5 contiguous amino
acids from the LSR transmembrane domain.

TABLE D

SEQ ID NO:	Amino acid sequence	Description
95	IQVTVSNPYHVILFQPVTLPCYQMTSTPTQPIVIWKYSFCRDRIADAFSPASVDNQLNAQLAAGNPGYNPYVEQCDSVRTVRVVATKQGNVATLG DYYQGRRITITGNADLTFDQTAWGDSGVYCSVVSAQDLQGNNEAYA	LSR_IgV_domain aa 42-186 of seq id : 11, 13, 15, 16, 17, 18

-continued

DYYQGRRITITGMYAAGKAATSGVPSIYAPSTYAHLSPAKTPPPAMIP
MGPAYNGYPGGYPGDVDRSSSAGGQGSYVPLLRDTSVASVRSYRI
QASQQDDSMRVLVYMEKELANEDPSRPGPPSGRVERAMSEVTS LHEDD
WSRPSRGPALTPIRDEEWGGHSPRSPRGWDQEPAREQAGGWRARRPRA
RSVDALDDLTPSTAESGSRSPSTNGGRSRAYMPPRSRSRDDLYQDD
SRDFPFRSRDPHYDDFRSRERPPADPRSHHHRTRDPRDNGSRSGDL
PYDGRLLLEEAVRKKGSEERRRPKHEEEAYYPAPPYSETDSQASRER
RLKKNLALSRESLV;
SEQ ID NO: 50, LSR isoform F secreted variant
amino acid residues 42-552 (FIG. 1J):
IQVTVSNPYHVILFQPVTLPCYQMTSTPTQPIVIWKYSFCRDRIAD
AFSPASVDNQLNAQLAAGNPGYNPYVEQCDSVRTVRVVATKQGNVATLG
DYYQGRRITITGNADLTFDQTAWGDSGVYCSVVSAQDLQGNNEAYAE
IVLGRSGVAELLPGFQAGPIEVYAAGKAATSGVPSIYAPSTYAHLS
PAKTPPPAMIPMGPAYNGYPGGYPGDVDRSSSAGGQGSYVPLLRD
TSSVASVRSYRIQASQQDDSMRVLVYMEKELANFDPSPRGPPSGR
VERAMSEVTS LHEDDWSRPSRGPALTPIRDEEWGGHSPRSPRGWD
QEPAREQAGGWRARRPRARSVDALDDLTPSTAESGSRSPSTNGGR
SRAYMPPRSRS

Optionally, the fragment is of at least about 98, 99, 100,
101, 102 and so forth amino acids of the extracellular domain
of LSR protein, set forth in SEQ ID NO: 11, up to 180 amino
acids of the LY6G6F protein extracellular domain, optionally
including any integral value between 98 and 180 amino acids
in length. Preferably, the fragment is of at least about 98 up to
118 amino acids of the LSR protein extracellular domain,
optionally including any integral value between 98 and 118
amino acids in length. Also preferably the fragment is of at
least about 135 up to 155 amino acids of the LSR protein
extracellular domain, optionally including any integral value
between 135 and 155 amino acids in length. Also preferably
the fragment is of at least about 160 up to 180 amino acids of
the LSR protein extracellular domain, optionally including
any integral value between 160 and 180 amino acids in length.
More preferably, the fragment is about 108 or 145 or 170
amino acids. The LSR fragment protein according to at least
some embodiments of the invention may or may not include
a signal peptide sequence, and may or may not include 1, 2, 3,
4, or 5 contiguous amino acids from the LSR transmembrane
domain.

The LSR proteins contain an immunoglobulin domain
within the extracellular domain, the IgV domain (or V
domain), which is related to the variable domain of antibod-
ies. The Ig domain is shown in a box in FIGS. 1E, 1F, 1G, 1H,
and 1J, for SEQ ID NOs: 11, 13, 15, 16, and 18, respectively.
The Ig domain of the extracellular domain includes one dis-
ulfide bond formed between intradomain cysteine residues, as
is typical for this fold and may be important for structure-
function. In SEQ ID NO: 11 these cysteines are located at
residues 63 and 170.

In one embodiment, there is provided a soluble fragment of LSR, which may optionally be described as a first fusion partner, as for example in the below section on fusion proteins. Useful fragments are those that retain the ability to bind to their natural receptor or receptors and/or retain the ability to inhibit T cell activation. A LSR polypeptide that is a fragment of full-length LSR typically has at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 98 percent, 99 percent, 100 percent, or even more than 100 percent of the ability to bind its natural receptor(s) and/or of the ability to inhibit T cell activation as compared to full-length LSR. Soluble LSR polypeptide fragments are fragments of LSR polypeptides that may be shed, secreted or otherwise extracted from the producing cells. In other embodiments, the soluble fragments of LSR polypeptides include fragments of the LSR extracellular domain that retain LSR biological activity, such as fragments that retain the ability to bind to their natural receptor or receptors and/or retain the ability to inhibit T cell activation. The extracellular domain can include 1, 2, 3, 4, or 5 contiguous amino acids from the transmembrane domain, and/or 1, 2, 3, 4, or 5 contiguous amino acids from the signal sequence. Alternatively, the extracellular domain can have 1, 2, 3, 4, 5 or more amino acids removed from the C-terminus, N-terminus, or both.

In some embodiments the LSR extracellular domain polypeptide comprises the amino acid of the IgV domain as set forth in any one of SEQ ID NO: 95, or fragments or variants thereof, or the region between the conserved cysteines of the IgV domain located at residues 63 and 170 of the full-length protein SEQ ID NO:11, corresponding to the sequence set forth in SEQ ID NO: 102: CTYQMT-STPTQPIVIWKYKSFCDRIADAFSPAS-VDNQLNAQLAAGNPGYNPYVE CQDSVRTVRVAVAT-KQGNAVTGLDYYQGRRITITGNADLTDFDQTAWGDSGVYYC. In some further embodiments the LSR extracellular domain polypeptide consists essentially of the amino acid of the IgV domain as set forth in any one of SEQ ID NO: 95, and SEQ ID NO: 102.

Generally, the LSR polypeptide fragments are expressed from nucleic acids that include sequences that encode a signal sequence. The signal sequence is generally cleaved from the immature polypeptide to produce the mature polypeptide lacking the signal sequence. The signal sequence of LSR can be replaced by the signal sequence of another polypeptide using standard molecule biology techniques to affect the expression levels, secretion, solubility, or other property of the polypeptide. The signal peptide sequence that is used to replace the LSR signal peptide sequence can be any known in the art.

Optionally, the LSR ECD refers also to any one of the nucleic acid sequences encoding LSR ECD polypeptides, optionally to the nucleic acid sequences set forth in SEQ ID NO:40, 41, 132, 44, 155, 188, or fragments thereof and/or degenerative variants thereof, encoding LSR ECD polypeptides set forth in any one of SEQ ID NO:12, 14, 47, 48, 49, 50, respectively.

Optionally, the LSR ECD refers to orthologous ECD polypeptides. Optionally, the LSR ECD refers to mouse LSR ECD polypeptides, set forth in SEQ ID NOs:21, and/or a mouse LSR ECD-IgG2a-Fc-fused polypeptide, set forth in SEQ ID NOs:26. Variants of LY6G6F, VSIG10, TMEM25 and/or LSR Polypeptides

The present invention encompasses useful variants of LY6G6F, VSIG10, TMEM25 and/or LSR polypeptides including those that increase biological activity, as indicated

by any of the assays described herein, or that increase half life or stability of the protein. Soluble LY6G6F, VSIG10, TMEM25 and/or LSR proteins or fragments, or fusions thereof having LY6G6F, VSIG10, TMEM25 and/or LSR proteins activity, respectively, can be engineered to increase biological activity. In a further embodiment, the LY6G6F, VSIG10, TMEM25 and/or LSR proteins or fusion protein is modified with at least one amino acid substitution, deletion, or insertion that increases the binding of the molecule to an immune cell, for example a T cell, and transmits an inhibitory signal into the T cell.

Other optional variants are those LY6G6F, VSIG10, TMEM25 and/or LSR proteins that are engineered to selectively bind to one type of T cell versus other immune cells. For example, the LY6G6F, VSIG10, TMEM25 and/or LSR polypeptide can be engineered to bind optionally to Tregs, Th0, Th1, Th17, Th2 or Th22 cells. Preferential binding refers to binding that is at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or greater for one type of cell over another type of cell. Still other variants of LY6G6F, VSIG10, TMEM25 and/or LSR protein can be engineered to have reduced binding to immune cells relative to wildtype LY6G6F, VSIG10, TMEM25 and/or LSR protein, respectively. These variants can be used in combination with variants having stronger binding properties to modulate the immune response with a moderate impact.

Also optionally, variant LY6G6F, VSIG10, TMEM25 and/or LSR protein can be engineered to have an increased half-life relative to wildtype. These variants typically are modified to resist enzymatic degradation. Exemplary modifications include modified amino acid residues and modified peptide bonds that resist enzymatic degradation. Various modifications to achieve this are known in the art.

The LY6G6F protein (SEQ ID NO:1) also has the following non-silent SNPs (Single Nucleotide Polymorphism) as listed in Table E, (given according to their position(s) on the amino acid sequence, with the alternative amino acid listed the presence of SNPs in LY6G6F protein (SEQ ID NO:1) sequence provides support for alternative sequence(s) of this protein according to the present invention. SEQ ID NO:58 is an example of such a alternative sequence, with alternative amino-acids, using part of the SNPs below

TABLE E

Amino acid mutations	
SNP position(s) on amino acid sequence	Alternative amino acid(s)
34	P -> Q
39	P -> S
107	A -> T
167	R -> K

The LSR protein (SEQ ID NO:11) also has the following non-silent SNPs (Single Nucleotide Polymorphism) as listed in Table F, (given according to their position(s) on the amino acid sequence, with the alternative amino acid listed; the presence of SNPs in LSR protein (SEQ ID NO:11) sequence provides support for alternative sequence(s) of this protein according to the present invention. SEQ ID NO:143 is an example of such a alternative sequence, with alternative amino-acids, using part of the SNPs below

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TABLE F

Amino acid mutations	
SNP position(s) on amino acid sequence	Alternative amino acid(s)
209	I -> M
211	D -> G
260	L -> R
315	S -> N
382	A -> G
591	N -> D

The VSIG10 protein (SEQ ID NO:3) also has the following non-silent SNPs (Single Nucleotide Polymorphism) as listed in Table G, (given according to their position(s) on the amino acid sequence, with the alternative amino acid listed; the presence of SNPs in VSIG10 protein (SEQ ID NO:3) sequence provides support for alternative sequence(s) of this protein according to the present invention.

TABLE G

Amino acid mutations	
SNP position(s) on amino acid sequence	Alternative amino acid(s)
333	V -> M
435	H -> Y

The TMEM25 protein (SEQ ID NO:7) also has the following non-silent SNPs (Single Nucleotide Polymorphism) as listed in Table H, (given according to their position(s) on the amino acid sequence, with the alternative amino acid listed; the presence of SNPs in TMEM25 protein (SEQ ID NO:7) sequence provides support for alternative sequence(s) of this protein according to the present invention.

TABLE H

Amino acid mutations	
SNP position(s) on amino acid sequence	Alternative amino acid(s)
25	W -> C
342	Q -> R

Various aspects of the invention are described in further detail in the following subsections.

Nucleic Acids

A "nucleic acid fragment" or an "oligonucleotide" or a "polynucleotide" are used herein interchangeably to refer to a polymer of nucleic acid residues. A polynucleotide sequence of the present invention refers to a single or double stranded nucleic acid sequences which is isolated and provided in the form of an RNA sequence, a complementary polynucleotide sequence (cDNA), a genomic polynucleotide sequence and/or a composite polynucleotide sequences (e.g., a combination of the above).

Thus, the present invention encompasses nucleic acid sequences described hereinabove; fragments thereof, sequences hybridizable therewith, sequences homologous thereto [e.g., at least 90%, at least 95, 96, 97, 98 or 99% or more identical to the nucleic acid sequences set forth herein], sequences encoding similar polypeptides with different codon usage, altered sequences characterized by mutations, such as deletion, insertion or substitution of one or more nucleotides, either naturally occurring or man induced, either

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randomly or in a targeted fashion. The present invention also encompasses homologous nucleic acid sequences (i.e., which form a part of a polynucleotide sequence of the present invention), which include sequence regions unique to the polynucleotides of the present invention.

Thus, the present invention also encompasses polypeptides encoded by the polynucleotide sequences of the present invention. The present invention also encompasses homologues of these polypeptides, such homologues can be at least 90%, at least 95, 96, 97, 98 or 99% or more homologous to the amino acid sequences set forth below, as can be determined using BlastP software of the National Center of Biotechnology Information (NCBI) using default parameters. As mentioned hereinabove, biomolecular sequences of the present invention can be efficiently utilized as tissue or pathological markers and as putative drugs or drug targets for treating or preventing a disease.

Oligonucleotides designed for carrying out the methods of the present invention for any of the sequences provided herein (designed as described above) can be generated according to any oligonucleotide synthesis method known in the art such as enzymatic synthesis or solid phase synthesis. Oligonucleotides used according to this aspect of the present invention are those having a length selected from a range of about 10 to about 200 bases preferably about 15 to about 150 bases, more preferably about 20 to about 100 bases, most preferably about 20 to about 50 bases.

The oligonucleotides of the present invention may comprise heterocyclic nucleosides consisting of purines and the pyrimidines bases, bonded in a 3' to 5' phosphodiester linkage.

Preferable oligonucleotides are those modified in either backbone, internucleoside linkages or bases, as is broadly described hereinunder. Such modifications can oftentimes facilitate oligonucleotide uptake and resistivity to intracellular conditions.

Specific examples of preferred oligonucleotides useful according to this aspect of the present invention include oligonucleotides containing modified backbones or non-natural internucleoside linkages. Oligonucleotides having modified backbones include those that retain a phosphorus atom in the backbone, as disclosed in U.S. Pat. Nos. 4,469,863; 4,476,301; 5,023,243; 5,177,196; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,306; 5,550,111; 5,563,253; 5,571,799; 5,587,361; and 5,625,050.

Preferred modified oligonucleotide backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkyl phosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts and free acid forms can also be used.

Alternatively, modified oligonucleotide backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar

portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH₂ component parts, as disclosed in U.S. Pat. Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,264,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,610,289; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; and 5,677,439.

Other oligonucleotides which can be used according to the present invention, are those modified in both sugar and the internucleoside linkage, i.e., the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for complementation with the appropriate polynucleotide target. An example for such an oligonucleotide mimetic, includes peptide nucleic acid (PNA). A PNA oligonucleotide refers to an oligonucleotide where the sugar-backbone is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The bases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. United States patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Pat. Nos. 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference. Other backbone modifications, which can be used in the present invention are disclosed in U.S. Pat. No. 6,303,374.

Oligonucleotides of the present invention may also include base modifications or substitutions. As used herein, "unmodified" or "natural" bases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified bases include but are not limited to other synthetic and natural bases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine and 3-deazaadenine. Further bases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in *The Concise Encyclopedia Of Polymer Science and Engineering*, pages 858-859, Kroschwitz, J. I., ed. John Wiley & Sons, 1990, those disclosed by Englisch et al., *Angewandte Chemie, International Edition*, 1991, 30, 613, and those disclosed by Sanghvi, Y. S., Chapter 15, *Antisense Research and Applications*, pages 289-302, Crooke, S. T. and Lebleu, B., ed., CRC Press, 1993. Such bases are particularly useful for increasing the binding affinity of the oligomeric compounds according to at least some embodiments of the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2° C. [Sanghvi Y S et al. (1993) *Antisense Research and Applications*, CRC Press, Boca Raton 276-278] and are presently preferred base sub-

stitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

Another modification of the oligonucleotides according to at least some embodiments of the invention involves chemically linking to the oligonucleotide one or more moieties or conjugates, which enhance the activity, cellular distribution or cellular uptake of the oligonucleotide. Such moieties include but are not limited to lipid moieties such as a cholesterol moiety, cholic acid, a thioether, e.g., hexyl-5-tritylthiol, a thiocholesterol, an aliphatic chain, e.g., dodecandiol or undecyl residues, a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycerol-3-H-phosphonate, a polyamine or a polyethylene glycol chain, or adamantane acetic acid, a palmitoyl moiety, or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety, as disclosed in U.S. Pat. No. 6,303,374.

It is not necessary for all positions in a given oligonucleotide molecule to be uniformly modified, and in fact more than one of the aforementioned modifications may be incorporated in a single compound or even at a single nucleoside within an oligonucleotide.

Peptides

The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an analog or mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers. Polypeptides can be modified, e.g., by the addition of carbohydrate residues to form glycoproteins. The terms "polypeptide," "peptide" and "protein" include glycoproteins, as well as non-glycoproteins.

Polypeptide products can be biochemically synthesized such as by employing standard solid phase techniques. Such methods include exclusive solid phase synthesis, partial solid phase synthesis methods, fragment condensation, classical solution synthesis. These methods are preferably used when the peptide is relatively short (i.e., 10 kDa) and/or when it cannot be produced by recombinant techniques (i.e., not encoded by a nucleic acid sequence) and therefore involves different chemistry.

Solid phase polypeptide synthesis procedures are well known in the art and further described by John Morrow Stewart and Janis Dillaha Young, *Solid Phase Peptide Syntheses* (2nd Ed., Pierce Chemical Company, 1984).

Synthetic polypeptides can be purified by preparative high performance liquid chromatography [Creighton T. (1983) *Proteins, structures and molecular principles*. WH Freeman and Co. N.Y.] and the composition of which can be confirmed via amino acid sequencing.

In cases where large amounts of a polypeptide are desired, it can be generated using recombinant techniques such as described by Bitter et al., (1987) *Methods in Enzymol.* 153: 516-544, Studier et al. (1990) *Methods in Enzymol.* 185:60-89, Brisson et al. (1984) *Nature* 310:511-514, Takamatsu et al. (1987) *EMBO J.* 6:307-311, Coruzzi et al. (1984) *EMBO J.* 3:1671-1680 and Brogli et al., (1984) *Science* 224:838-843, Gurley et al. (1986) *Mol. Cell. Biol.* 6:559-565.

It will be appreciated that peptides identified according to the teachings of the present invention may be degradation products, synthetic peptides or recombinant peptides as well as peptidomimetics, typically, synthetic peptides and peptoids and semipeptoids which are peptide analogs, which may have, for example, modifications rendering the peptides more stable while in a body or more capable of penetrating into cells. Such modifications include, but are not limited to N terminus modification, C terminus modification, peptide

bond modification, including, but not limited to, CH₂-NH, CH₂-S, CH₂-S=O, O=C-NH, CH₂-O, CH₂-CH₂, S=C-NH, CH=CH or CF=CH, backbone modifications, and residue modification. Methods for preparing peptidomimetic compounds are well known in the art and are specified, for example, in Quantitative Drug Design, C. A. Ramsden Gd., Chapter 17.2, F. Choplin Pergamon Press (1992), which is incorporated by reference as if fully set forth herein. Further details in this respect are provided hereinafter.

Peptide bonds (—CO—NH—) within the peptide may be substituted, for example, by N-methylated bonds (—N(CH₃)-CO—), ester bonds (—C(R)H—C—O—O—C(R)—N—), ketomethylen bonds (—CO—CH₂—), α -aza bonds (—NH—N(R)—CO—), wherein R is any alkyl, e.g., methyl, carba bonds (—CH₂-NH—), hydroxyethylene bonds (—CH(OH)—CH₂—), thioamide bonds (—CS—NH—), olefinic double bonds (—CH=CH—), retro amide bonds (—NH—CO—), peptide derivatives (—N(R)—CH₂-CO—), wherein R is the “normal” side chain, naturally presented on the carbon atom.

These modifications can occur at any of the bonds along the peptide chain and even at several (2-3) at the same time.

Natural aromatic amino acids, Trp, Tyr and Phe, may be substituted by synthetic non-natural acid such as Phenylglycine, TIC, naphthylelanine (Nol), ring-methylated derivatives of Phe, halogenated derivatives of Phe or o-methyl-Tyr.

In addition to the above, the peptides of the present invention may also include one or more modified amino acids or one or more non-amino acid monomers (e.g. fatty acids, complex carbohydrates etc).

As used herein in the specification and in the claims section below the term “amino acid” or “amino acids” is understood to include the 20 naturally occurring amino acids; those amino acids often modified post-translationally in vivo, including, for example, hydroxyproline, phosphoserine and phosphothreonine; and other unusual amino acids including, but not limited to, 2-aminoadipic acid, hydroxylysine, isodesmosine, nor-valine, nor-leucine and ornithine. Furthermore, the term “amino acid” includes both D- and L-amino acids.

Since the peptides of the present invention are preferably utilized in therapeutics which require the peptides to be in soluble form, the peptides of the present invention preferably include one or more non-natural or natural polar amino acids, including but not limited to serine and threonine which are capable of increasing peptide solubility due to their hydroxyl-containing side chain.

Expression Systems

To enable cellular expression of the polynucleotides of the present invention, a nucleic acid construct according to the present invention may be used, which includes at least a coding region of one of the above nucleic acid sequences, and further includes at least one cis acting regulatory element. As used herein, the phrase “cis acting regulatory element” refers to a polynucleotide sequence, preferably a promoter, which binds a trans acting regulator and regulates the transcription of a coding sequence located downstream thereto.

Any suitable promoter sequence can be used by the nucleic acid construct of the present invention.

Preferably, the promoter utilized by the nucleic acid construct of the present invention is active in the specific cell population transformed. Examples of cell type-specific and/or tissue-specific promoters include promoters such as albumin that is liver specific [Pinkert et al., (1987) Genes Dev. 1:268-277], lymphoid specific promoters [Calame et al., (1988) Adv. Immunol. 43:235-275]; in particular promoters of T-cell receptors [Winoto et al., (1989) EMBO J. 8:729-733] and immunoglobulins; [Banerji et al. (1983) Cell 33729-

740], neuron-specific promoters such as the neurofilament promoter [Byrne et al. (1989) Proc. Natl. Acad. Sci. USA 86:5473-5477], pancreas-specific promoters [Edlunch et al. (1985) Science 230:912-916] or mammary gland-specific promoters such as the milk whey promoter (U.S. Pat. No. 4,873,316 and European Application Publication No. 264,166). The nucleic acid construct of the present invention can further include an enhancer, which can be adjacent or distant to the promoter sequence and can function in up regulating the transcription therefrom.

The nucleic acid construct of the present invention preferably further includes an appropriate selectable marker and/or an origin of replication. Preferably, the nucleic acid construct utilized is a shuttle vector, which can propagate both in *E. coli* (wherein the construct comprises an appropriate selectable marker and origin of replication) and be compatible for propagation in cells, or integration in a gene and a tissue of choice. The construct according to the present invention can be, for example, a plasmid, a bacmid, a phagemid, a cosmid, a phage, a virus or an artificial chromosome.

Examples of suitable constructs include, but are not limited to, pcDNA3, pcDNA3.1 (+/-), pGL3, PzeoSV2 (+/-), pDisplay, pEF/myc/cyto, pCMV/myc/cyto each of which is commercially available from Invitrogen Co. (www.invitrogen.com). Examples of retroviral vector and packaging systems are those sold by Clontech, San Diego, Calif., including Retro-X vectors pLNCX and pLXSN, which permit cloning into multiple cloning sites and the transgene is transcribed from CMV promoter. Vectors derived from Mo-MuLV are also included such as pBabe, where the transgene will be transcribed from the 5'LTR promoter.

Currently preferred in vivo nucleic acid transfer techniques include transfection with viral or non-viral constructs, such as adenovirus, lentivirus, Herpes simplex I virus, or adeno-associated virus (AAV) and lipid-based systems. Useful lipids for lipid-mediated transfer of the gene are, for example, DOTMA, DOPE, and DC-Chol [Tonkinson et al., Cancer Investigation, 14(1): 54-65 (1996)]. The most preferred constructs for use in gene therapy are viruses, most preferably adenoviruses, AAV, lentiviruses, or retroviruses. A viral construct such as a retroviral construct includes at least one transcriptional promoter/enhancer or locus-defining elements, or other elements that control gene expression by other means such as alternate splicing, nuclear RNA export, or post-translational modification of messenger. Such vector constructs also include a packaging signal, long terminal repeats (LTRs) or portions thereof, and positive and negative strand primer binding sites appropriate to the virus used, unless it is already present in the viral construct. In addition, such a construct typically includes a signal sequence for secretion of the peptide from a host cell in which it is placed. Preferably the signal sequence for this purpose is a mammalian signal sequence or the signal sequence of the polypeptides of the present invention. Optionally, the construct may also include a signal that directs polyadenylation, as well as one or more restriction sites and a translation termination sequence. By way of example, such constructs will typically include a 5' LTR, a tRNA binding site, a packaging signal, an origin of second-strand DNA synthesis, and a 3' LTR or a portion thereof. Other vectors can be used that are non-viral, such as cationic lipids, polylysine, and dendrimers.

Recombinant Expression Vectors and Host Cells

Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding a protein according to at least some embodiments of the invention, or derivatives, fragments, analogs or homologs thereof. As used herein, the term “vector” refers to a nucleic acid

molecule capable of transporting another nucleic acid to which it has been linked. Examples of vector types are plasmids and viral vectors. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively-linked. Such vectors are referred to herein as "expression vectors". The invention is intended to include such forms of expression vectors, such as plasmids, viral vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The recombinant expression vectors according to at least some embodiments of the invention comprise a nucleic acid according to at least some embodiments of the invention in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, that is operatively-linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably-linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequences in a manner that allows for expression of the nucleotide sequence (e.g., in an in vitro transcription/translation system or in a host cell when the vector is introduced into the host cell).

The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (e.g., polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, Calif. (1990). Regulatory sequences include those that direct constitutive expression of a nucleotide sequence in many types of host cell and those that direct expression of the nucleotide sequence only in certain host cells (e.g., tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. The expression vectors according to at least some embodiments of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein.

The recombinant expression vectors according to at least some embodiments of the invention can be designed for production of variant proteins in prokaryotic or eukaryotic cells. For example, proteins according to at least some embodiments of the invention can be expressed in bacterial cells such as *Escherichia coli*, insect cells (using baculovirus expression vectors) yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, Calif. (1990). Alternatively, the recombinant expression vector can be transcribed and translated in vitro, for example using T7 promoter regulatory sequences and T7 polymerase.

Expression of proteins in prokaryotes is most often carried out in *Escherichia coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, to the amino or C terminus of the recombinant protein. Such fusion vectors typically

serve three purposes: (i) to increase expression of recombinant protein; (ii) to increase the solubility of the recombinant protein; and (iii) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin, PreScission, TEV and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith and Johnson, 1988. *Gene* 67: 31-40), pMAL (New England Biolabs, Beverly, Mass.) and pRIT5 (Pharmacia, Piscataway, N.J.) that fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

In another embodiment, the expression vector encoding for the protein of the invention is a yeast expression vector. Examples of vectors for expression in yeast *Saccharomyces cerevisiae* include pYepSec1 (Baldari, et al., 1987. *EMBO J.* 6: 229-234), pMFa (Kurj an and Herskowitz, 1982. *Cell* 30: 933-943), pJRY88 (Schultz et al., 1987. *Gene* 54: 113-123), pYES2 (Invitrogen Corporation, San Diego, Calif.), and picZ (Invitrogen Corp, San Diego, Calif.).

Alternatively, polypeptides of the present invention can be produced in insect cells using baculovirus expression vectors. Baculovirus vectors available for expression of proteins in cultured insect cells (e.g., SF9 cells) include the pAc series (Smith, et al., 1983. *Mol. Cell. Biol.* 3: 2156-2165) and the pVL series (Lucklow and Summers, 1989. *Virology* 170: 31-39).

In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, 1987. *Nature* 329: 840) and pMT2PC (Kaufman, et al., 1987. *EMBO J.* 6: 187-195), pIRESpuro (Clontech), pUB6 (Invitrogen), pCEP4 (Invitrogen) pREP4 (Invitrogen), pcDNA3 (Invitrogen). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, adenovirus 2, cytomegalovirus, Rous Sarcoma Virus, and simian virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see, e.g., Chapters 16 and 17 of Sambrook, et al., *Molecular Cloning: A Laboratory Manual*. 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989.

In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (e.g., tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert, et al., 1987. *Genes Dev.* 1: 268-277), lymphoid-specific promoters (Calame and Eaton, 1988. *Adv. Immunol.* 43: 235-275), in particular promoters of T cell receptors (Winoto and Baltimore, 1989. *EMBO J.* 8: 729-733) and immunoglobulins (Banerji, et al., 1983. *Cell* 33: 729-740; Queen and Baltimore, 1983. *Cell* 33: 741-748), neuron-specific promoters (e.g., the neurofilament promoter; Byrne and Ruddle, 1989. *Proc. Natl. Acad. Sci. USA* 86: 5473-5477), pancreas-specific promoters (Edlund, et al., 1985. *Science* 230: 912-916), and mammary gland-specific promoters (e.g., milk whey promoter; U.S. Pat. No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, e.g., the murine hox promoters (Kessel and

Gruss, 1990. Science 249: 374-379) and the alpha-fetoprotein promoter (Campes and Tilghman, 1989. Genes Dev. 3: 537-546).

According to at least some embodiments the invention further provides a recombinant expression vector comprising a DNA molecule according to at least some embodiments of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operatively-linked to a regulatory sequence in a manner that allows for expression (by transcription of the DNA molecule) of an RNA molecule that is antisense to mRNA encoding for protein according to at least some embodiments of the invention. Regulatory sequences operatively linked to a nucleic acid cloned in the antisense orientation can be chosen that direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen that direct constitutive, tissue specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes see, e.g., Weintraub, et al., "Antisense RNA as a molecular tool for genetic analysis," Reviews-Trends in Genetics, Vol. 1(1) 1986.

According to at least some embodiments the invention pertains to host cells into which a recombinant expression vector according to at least some embodiments of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

A host cell can be any prokaryotic or eukaryotic cell. For example, protein according to at least some embodiments of the invention can be produced in bacterial cells such as *E. coli*, insect cells, yeast, plant or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS or 293 cells). Other suitable host cells are known to those skilled in the art.

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (e.g., DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, et al. (Molecular Cloning: A Laboratory Manual. 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (e.g., resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Various selectable markers include those that confer resistance to drugs, such as G418, hygromycin, puromycin, blasticidin and

methotrexate. Nucleic acids encoding a selectable marker can be introduced into a host cell on the same vector as that encoding protein according to at least some embodiments of the invention or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (e.g., cells that have incorporated the selectable marker gene will survive, while the other cells die).

A host cell according to at least some embodiments of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (i.e., express) protein according to at least some embodiments of the invention. Accordingly, the invention further provides methods for producing proteins according to at least some embodiments of the invention using the host cells according to at least some embodiments of the invention. In one embodiment, the method comprises culturing the host cell of the present invention (into which a recombinant expression vector encoding protein according to at least some embodiments of the invention has been introduced) in a suitable medium such that the protein according to at least some embodiments of the invention is produced. In another embodiment, the method further comprises isolating protein according to at least some embodiments of the invention from the medium or the host cell.

For efficient production of the protein, it is preferable to place the nucleotide sequences encoding the protein according to at least some embodiments of the invention under the control of expression control sequences optimized for expression in a desired host. For example, the sequences may include optimized transcriptional and/or translational regulatory sequences (such as altered Kozak sequences).

It should be noted, that according to at least some embodiments of the present invention the LY6G6F, VSIG10, TMEM25 and/or LSR proteins according to at least some embodiments of the invention may be isolated as naturally-occurring polypeptides, or from any source whether natural, synthetic, semi-synthetic or recombinant. Accordingly, the LY6G6F, VSIG10, TMEM25 and/or LSR proteins may be isolated as naturally-occurring proteins from any species, particularly mammalian, including bovine, ovine, porcine, murine, equine, and preferably human. Alternatively, the LY6G6F, VSIG10, TMEM25 and/or LSR proteins may be isolated as recombinant polypeptides that are expressed in prokaryote or eukaryote host cells, or isolated as a chemically synthesized polypeptide.

A skilled artisan can readily employ standard isolation methods to obtain isolated LY6G6F, VSIG10, TMEM25 and/or LSR proteins. The nature and degree of isolation will depend on the source and the intended use of the isolated molecules.

Transgenic Animals and Plants

According to at least some embodiments the invention also provides transgenic non-human animals and transgenic plants comprising one or more nucleic acid molecules according to at least some embodiments of the invention that may be used to produce the polypeptides according to at least some embodiments of the invention. The polypeptides can be produced in and recovered from tissue or bodily fluids, such as milk, blood or urine, of goats, cows, horses, pigs, rats, mice, rabbits, hamsters or other mammals. See, e.g., U.S. Pat. Nos. 5,827,690, 5,756,687, 5,750,172, and 5,741,957.

Non-human transgenic animals and transgenic plants are produced by introducing one or more nucleic acid molecules according to at least some embodiments of the invention into the animal or plant by standard transgenic techniques. The transgenic cells used for making the transgenic animal can be embryonic stem cells, somatic cells or fertilized egg cells.

The transgenic non-human organisms can be chimeric, non-chimeric heterozygotes, and nonchimeric homozygotes. See, e.g., Hogan et al. *Manipulating the Mouse Embryo: A Laboratory Manual* 2ed. Cold Spring Harbor Press (1999); Jackson et al., *Mouse Genetics and Transgenics: A Practical Approach*, Oxford University Press (2000); and Pinkert, *Transgenic Animal Technology: A Laboratory Handbook*, Academic Press (1999).

Gene Therapy

According to at least some embodiments of the present invention, nucleic acid sequences encoding soluble LY6G6F, VSIG10, TMEM25 and/or LSR proteins can be used in gene therapy for treatment of infectious disorders, and/or immune related disorders, and or cancer.

As used herein, "gene therapy" is a process to treat a disease by genetic manipulation so that a sequence of nucleic acid is transferred into a cell, the cell then expressing any genetic product encoded by the nucleic acid. For example, as is well known by those skilled in the art, nucleic acid transfer may be performed by inserting an expression vector containing the nucleic acid of interest into cells *ex vivo* or *in vitro* by a variety of methods including, for example, calcium phosphate precipitation, diethylaminoethyl dextran, polyethylene glycol (PEG), electroporation, direct injection, lipofection or viral infection (Sambrook et al., *Molecular Cloning: A Laboratory Manual* (Cold Spring Harbor Laboratory Press 1989); Kriegler M. *Gene Transfer and Expression: A Laboratory Manual* (W. H. Freeman and Co, New York, N.Y., 1993) and Wu, *Methods in Enzymology* (Academic Press, New York, 1993). Alternatively, nucleic acid sequences of interest may be transferred into a cell *in vivo* in a variety of vectors and by a variety of methods including, for example, direct administration of the nucleic acid into a subject, or insertion of the nucleic acid into a viral vector and infection of the subject with the virus. Other methods used for *in vivo* transfer include encapsulation of the nucleic acid into liposomes, and direct transfer of the liposomes, or liposomes combined with a hemagglutinating Sendai virus, to a subject. The transfected or infected cells express the protein products encoded by the nucleic acid in order to ameliorate a disease or the symptoms of a disease.

Antibodies and Immune System Response

As used herein, the terms "immunologic", "immunological" or "immune" response is the development of a beneficial humoral (antibody mediated) and/or a cellular (mediated by antigen-specific T cells or their secretion products) response directed against a peptide in a recipient patient. Such a response can be an active response induced by administration of immunogen or a passive response induced by administration of antibody or primed T-cells. Without wishing to be limited by a single hypothesis, a cellular immune response is elicited by the presentation of polypeptide epitopes in association with Class I or Class II MHC molecules to activate antigen-specific CD4+ T helper cells and/or CD8+ cytotoxic T cells. The response may also involve activation of monocytes, macrophages, NK cells, basophils, dendritic cells, astrocytes, microglia cells, eosinophils, activation or recruitment of neutrophils or other components of innate immunity. The presence of a cell-mediated immunological response can be determined by proliferation assays (CD4+ T cells) or CTL (cytotoxic T lymphocyte) assays. The relative contributions of humoral and cellular responses to the protective or therapeutic effect of an immunogen can be distinguished by separately isolating antibodies and T-cells from an immunized syngeneic animal and measuring protective or therapeutic effect in a second subject.

An "immunogenic agent" or "immunogen" is capable of inducing an immunological response against itself on administration to a mammal, optionally in conjunction with an adjuvant.

A "signal, transduction pathway" refers to the biochemical relationship between varieties of signal transduction molecules that play a role in the transmission of a signal from one portion of a cell to another portion of a cell.

As used herein, the phrase "cell surface receptor" includes, for example, molecules and complexes of molecules capable of receiving a signal and the transmission of such a signal across the plasma membrane of a cell.

The term "antibody" as referred to herein includes whole polyclonal and monoclonal antibodies and any antigen binding fragment (i.e., "antigen-binding portion") or single chains thereof. An "antibody" refers to a glycoprotein comprising at least two heavy (H) chains and two light (L) chains interconnected by disulfide bonds, or an antigen binding portion thereof. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (C1q) of the classical complement system.

The term "antigen-binding portion" of an antibody (or simply "antibody portion"), as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., LY6G6F, VSIG10, TMEM25 and/or LSR molecules, and/or a fragment thereof). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the V Light, V Heavy, Constant light (CL) and CH1 domains; (ii) a F(ab')₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., (1989) *Nature* 341:544-546), which consists of a VH domain; and (vi) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv); see e.g., Bird et al. (1988) *Science* 242:423-426; and Huston et al. (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term "antigen-binding portion" of an antibody. These antibody fragments are obtained using conventional techniques

known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

An "isolated antibody", as used herein, is intended to refer to an antibody that is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody that specifically binds LY6G6F, VSIG10, TMEM25 or LSR proteins and/or fragments thereof, and is substantially free of antibodies that specifically bind antigens other than LY6G6F, VSIG10, TMEM25 or LSR, respectively. An isolated antibody that specifically binds LY6G6F, VSIG10, TMEM25 or LSR proteins may, however, have cross-reactivity to other antigens, such as LY6G6F, VSIG10, TMEM25 or LSR molecules from other species, respectively. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

The terms "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope.

The term "human antibody", as used herein, is intended to include antibodies having variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. Furthermore, if the antibody contains a constant region, the constant region also is derived from human germline immunoglobulin sequences. The human antibodies according to at least some embodiments of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*). However, the term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

The term "human monoclonal antibody" refers to antibodies displaying a single binding specificity which have variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. In one embodiment, the human monoclonal antibodies are produced by a hybridoma which includes a B cell obtained from a transgenic nonhuman animal, e.g., a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell.

The term "recombinant human antibody", as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom (described further below), (b) antibodies isolated from a host cell transformed to express the human antibody, e.g., from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable regions in which the framework and CDR regions are derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human

germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

As used herein, "isotype" refers to the antibody class (e.g., IgM or IgG1) that is encoded by the heavy chain constant region genes.

The phrases "an antibody recognizing an antigen" and "an antibody specific for an antigen" are used interchangeably herein with the term "an antibody which binds specifically to an antigen."

As used herein, an antibody that "specifically binds to human LY6G6F, VSIG10, TMEM25 or LSR proteins" is intended to refer to an antibody that binds to LY6G6F, VSIG10, TMEM25 or LSR proteins, respectively, such as for example, one with a KD of 5×10^{-8} M, 3×10^{-8} M, 1×10^{-9} M or less.

The term "K-assoc" or "Ka", as used herein, is intended to refer to the association rate of a particular antibody-antigen interaction, whereas the term "Kdiss" or "Kd," as used herein, is intended to refer to the dissociation rate of a particular antibody-antigen interaction. The term "KD", as used herein, is intended to refer to the dissociation constant, which is obtained from the ratio of Kd to Ka (i.e., Kd/Ka) and is expressed as a molar concentration (M). KD values for antibodies can be determined using methods well established in the art. A preferred method for determining the KD of an antibody is by using surface Plasmon resonance, preferably using a biosensor system such as a Biacore® system.

As used herein, the term "high affinity" for an IgG antibody refers to an antibody having a KD of 10^{-8} M or less, more preferably 10^{-9} M or less and even more preferably 10^{-10} M or less for a target antigen. However, "high affinity" binding can vary for other antibody isotypes. For example, "high affinity" binding for an IgM isotype refers to an antibody having a KD of 10^{-7} M or less, more preferably 10^{-8} M or less.

As used herein, the term "subject" or "patient" includes any human or nonhuman animal. The term "nonhuman animal" includes all vertebrates, e.g., mammals and non-mammals, such as nonhuman primates, sheep, dogs, cats, horses, cows, chickens, amphibians, reptiles, etc.

Anti-LY6G6F, Anti-VSIG10, Anti-TMEM25 and Anti-LSR Antibodies

The antibodies according to at least some embodiments of the invention including those having the particular germline sequences, homologous antibodies, antibodies with conservative modifications, engineered and modified antibodies are characterized by particular functional features or properties of the antibodies. For example, the antibodies bind specifically to human LY6G6F, VSIG10, TMEM25 or LSR. Preferably, an antibody according to at least some embodiments of the invention binds to corresponding LY6G6F, VSIG10, TMEM25 or LSR with high affinity, for example with a KD of 10^{-8} M or less or 10^{-9} M or less or even 10^{-10} M or less. The anti-LY6G6F, anti-VSIG10, anti-TMEM25 and anti-LSR antibodies according to at least some embodiments of the present invention preferably exhibit one or more of the following characteristics:

(i) binds to corresponding human LY6G6F, VSIG10, TMEM25 or LSR with a KD of 5×10^{-8} M or less;

(ii) modulates (enhances or inhibits) B7 immune costimulation and related activities and functions such as T cell responses involved in antitumor immunity and autoimmunity, and/or

(iii) binds to LY6G6F, VSIG10, TMEM25 or LSR antigen expressed by cancer cells including for example melanoma, cancers of liver, renal, brain, breast, colon, lung, ovary, pancreas, prostate, stomach, multiple myeloma, and hematopoietic

etic cancer, including but not limited to lymphoma (Hodgkin's and non Hodgkin's), acute and chronic lymphoblastic leukemia and acute and chronic myeloid leukemia., but does not substantially bind to normal cells. In addition, preferably these antibodies and conjugates thereof will be effective in eliciting selective killing of such cancer cells and for modulating immune responses involved in autoimmunity and cancer.

More preferably, the antibody binds to corresponding human LY6G6F, VSIG10, TMEM25 or LSR antigen with a KD of 3×10^{-8} M or less, or with a KD of 1×10^{-9} M or less, or with a KD of 0.1×10^{-9} M or less, or with a KD of 0.05×10^{-9} M or less or with a KD of between 1×10^{-9} and 1×10^{-11} M.

Standard assays to evaluate the binding ability of the antibodies toward LY6G6F, VSIG10, TMEM25 or LSR are known in the art, including for example, ELISAs, Western blots and RIAs. Suitable assays are described in detail in the Examples. The binding kinetics (e.g., binding affinity) of the antibodies also can be assessed by standard assays known in the art, such as by Biacore analysis.

Upon production of anti-LY6G6F, anti-VSIG10, anti-TMEM25 and anti-LSR antibody sequences from antibodies can bind to LY6G6F, VSIG10, TMEM25 or LSR the VH and VL sequences can be "mixed and matched" to create other anti-LY6G6F, anti-VSIG10, anti-TMEM25 and anti-LSR, binding molecules according to at least some embodiments of the invention. LY6G6F, VSIG10, TMEM25 or LSR binding of such "mixed and matched" antibodies can be tested using the binding assays described above. e.g., ELISAs). Preferably, when VH and VL chains are mixed and matched, a VH sequence from a particular VH/VL pairing is replaced with a structurally similar VH sequence. Likewise, preferably a VL sequence from a particular VH/VL pairing is replaced with a structurally similar VL sequence. For example, the VH and VL sequences of homologous antibodies are particularly amenable for mixing and matching.

Antibodies Having Particular Germline Sequences

In certain embodiments, an antibody of the invention comprises a heavy chain variable region from a particular germline heavy chain immunoglobulin gene and/or a light chain variable region from a particular germline light chain immunoglobulin gene.

As used herein, a human antibody comprises heavy or light chain variable regions that is "the product of" or "derived from" a particular germline sequence if the variable regions of the antibody are obtained from a system that uses human germline immunoglobulin genes. Such systems include immunizing a transgenic mouse carrying human immunoglobulin genes with the antigen of interest or screening a human immunoglobulin gene library displayed on phage with the antigen of interest. A human antibody that is "the product of" or "derived from" a human germline immunoglobulin sequence can be identified as such by comparing the amino acid sequence of the human antibody to the amino acid sequences of human germline immunoglobulins and selecting the human germline immunoglobulin sequence that is closest in sequence (i.e., greatest % identity) to the sequence of the human antibody.

A human antibody that is "the product of" or "derived from" a particular human germline immunoglobulin sequence may contain amino acid differences as compared to the germline sequence, due to, for example, naturally-occurring somatic mutations or intentional introduction of site-directed mutation. However, a selected human antibody typically is at least 90% identical in amino acids sequence to an amino acid sequence encoded by a human germline immunoglobulin gene and contains amino acid residues that iden-

tify the human antibody as being human when compared to the germline immunoglobulin amino acid sequences of other species (e.g., murine germline sequences). In certain cases, a human antibody may be at least 95, 96, 97, 98 or 99%, or even at least 96%, 97%, 98%, or 99% identical in amino acid sequence to the amino acid sequence encoded by the germline immunoglobulin gene. Typically, a human antibody derived from a particular human germline sequence will display no more than 10 amino acid differences from the amino acid sequence encoded by the human germline immunoglobulin gene. In certain cases, the human antibody may display no more than 5, or even no more than 4, 3, 2, or 1 amino acid difference from the amino acid sequence encoded by the germline immunoglobulin gene.

Homologous Antibodies

In yet another embodiment, an antibody of the invention comprises heavy and light chain variable regions comprising amino acid sequences that are homologous to isolated anti-LY6G6F, anti-VSIG10, anti-TMEM25 or anti-LSR amino acid sequences of preferred anti-LY6G6F, anti-VSIG10, anti-TMEM25 or anti-LSR antibodies, respectively, wherein the antibodies retain the desired functional properties of the parent anti-LY6G6F, anti-VSIG10, anti-TMEM25 or anti-LSR antibodies.

As used herein, the percent homology between two amino acid sequences is equivalent to the percent identity between the two sequences. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % homology = # of identical positions/total # of positions \times 100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm, as described in the non-limiting examples below.

The percent identity between two amino acid sequences can be determined using the algorithm of E. Meyers and W. Miller (Comput. Appl. Biosci., 4:11-17 (1988)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (J. Mol. Biol. 48:444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package (available commercially), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

Additionally or alternatively, the protein sequences of the present invention can further be used as a "query sequence" to perform a search against public databases to, for example, identify related sequences. Such searches can be performed using the XBLAST program (version 2.0) of Altschul, et al. (1990) J Mol. Biol. 215:403-10. BLAST protein searches can be performed with the XBLAST program, score=50, wordlength=3 to obtain amino acid sequences homologous to the antibody molecules according to at least some embodiments of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al., (1997) Nucleic Acids Res. 25(17): 3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used.

Antibodies with Conservative Modifications

In certain embodiments, an antibody of the invention comprises a heavy chain variable region comprising CDR1,

CDR2 and CDR3 sequences and a light chain variable region comprising CDR1, CDR2 and CDR3 sequences, wherein one or more of these CDR sequences comprise specified amino acid sequences based on preferred anti-LY6G6F, anti-VSIG10, anti-TMEM25 or anti-LSR antibodies isolated and produced using methods herein, or conservative modifications thereof, and wherein the antibodies retain the desired functional properties of the anti-LY6G6F, anti-VSIG10, anti-TMEM25 or anti-LSR antibodies according to at least some embodiments of the invention, respectively.

In various embodiments, the anti-LY6G6F, anti-VSIG10, anti-TMEM25 or anti-LSR antibody can be, for example, human antibodies, humanized antibodies or chimeric antibodies.

As used herein, the term "conservative sequence modifications" is intended to refer to amino acid modifications that do not significantly affect or alter the binding characteristics of the antibody containing the amino acid sequence. Such conservative modifications include amino acid substitutions, additions and deletions. Modifications can be introduced into an antibody according to at least some embodiments of the invention by standard techniques known in the art, such as site-directed mutagenesis and PCR-mediated mutagenesis. Conservative amino acid substitutions are ones in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, one or more amino acid residues within the CDR regions of an antibody according to at least some embodiments of the invention can be replaced with other amino acid residues from the same side chain family and the altered antibody can be tested for retained function (i.e., the functions set forth in (c) through (j) above) using the functional assays described herein.

Antibodies that Bind to the Same Epitope as Anti-LY6G6F, Anti-VSIG10, Anti-TMEM25 or Anti-LSR According to at Least Some Embodiments of the Invention.

In another embodiment, the invention provides antibodies that bind to preferred epitopes on human LY6G6F, VSIG10, TMEM25 or LSR which possess desired functional properties such as modulation of B7 co-stimulation and related functions. Other antibodies with desired epitope specificity may be selected and will have the ability to cross-compete for binding to LY6G6F, VSIG10, TMEM25 or LSR antigen with the desired antibodies.

Engineered and Modified Antibodies

An antibody according to at least some embodiments of the invention further can be prepared using an antibody having one or more of the VH and/or VL sequences derived from an anti-LY6G6F, anti-VSIG10, anti-TMEM25 or anti-LSR antibody starting material to engineer a modified antibody, which modified antibody may have altered properties from the starting antibody. An antibody can be engineered by modifying one or more residues within one or both variable regions (i.e., VH and/or VL), for example within one or more CDR regions and/or within one or more framework regions. Additionally or alternatively, an antibody can be engineered by modifying residues within the constant regions, for example to alter the effector functions of the antibody.

One type of variable region engineering that can be performed is CDR grafting. Antibodies interact with target antigens predominantly through amino acid residues that are located in the six heavy and light chain complementarity determining regions (CDRs). For this reason, the amino acid sequences within CDRs are more diverse between individual antibodies than sequences outside of CDRs. Because CDR sequences are responsible for most antibody-antigen interactions, it is possible to express recombinant antibodies that mimic the properties of specific naturally occurring antibodies by constructing expression vectors that include CDR sequences from the specific naturally occurring antibody grafted onto framework sequences from a different antibody with different properties (see, e.g., Riechmann, L. et al. (1998) *Nature* 332:323-327; Jones, P. et al. (1986) *Nature* 321:522-525; Queen, C. et al. (1989) *Proc. Natl. Acad. Sci. U.S.A.* 86:10029-10033; U.S. Pat. No. 5,225,539 to Winter, and U.S. Pat. Nos. 5,530,101; 5,585,089; 5,693,762 and 6,180,370 to Queen et al.)

Suitable framework sequences can be obtained from public DNA databases or published references that include germline antibody gene sequences. For example, germline DNA sequences for human heavy and light chain variable region genes can be found in the "VBase" human germline sequence database (available on the Internet), as well as in Kabat, E. A., et al. (1991) *Sequences of Proteins of Immunological Interest*, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; Tomlinson, I. M., et al. (1992) "The Repertoire of Human Germline VH Sequences Reveals about Fifty Groups of VH Segments with Different Hypervariable Loops" *J. Mol. Biol.* 227:776-798; and Cox, J. P. L. et al. (1994) "A Directory of Human Germline VH Segments Reveals a Strong Bias in their Usage" *Eur. J. Immunol.* 24:827-836; the contents of each of which are expressly incorporated herein by reference.

Another type of variable region modification is to mutate amino acid residues within the VH and/or VL CDR 1, CDR2 and/or CDR3 regions to thereby improve one or more binding properties (e.g., affinity) of the antibody of interest. Site-directed mutagenesis or PCR-mediated mutagenesis can be performed to introduce the mutations and the effect on antibody binding, or other functional property of interest, can be evaluated in appropriate in vitro or in vivo assays. Preferably conservative modifications (as discussed above) are introduced. The mutations may be amino acid substitutions, additions or deletions, but are preferably substitutions. Moreover, typically no more than one, two, three, four or five residues within a CDR region are altered.

Engineered antibodies according to at least some embodiments of the invention include those in which modifications have been made to framework residues within VH and/or VL, e.g. to improve the properties of the antibody. Typically such framework modifications are made to decrease the immunogenicity of the antibody. For example, one approach is to "backmutate" one or more framework residues to the corresponding germline sequence. More specifically, an antibody that has undergone somatic mutation may contain framework residues that differ from the germline sequence from which the antibody is derived. Such residues can be identified by comparing the antibody framework sequences to the germline sequences from which the antibody is derived.

In addition or alternative to modifications made within the framework or CDR regions, antibodies according to at least some embodiments of the invention may be engineered to include modifications within the Fc region, typically to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding,

and/or antigen-dependent cellular cytotoxicity. Furthermore, an antibody according to at least some embodiments of the invention may be chemically modified (e.g., one or more chemical moieties can be attached to the antibody) or be modified to alter its glycosylation, again to alter one or more functional properties of the antibody. Such embodiments are described further below. The numbering of residues in the Fc region is that of the EU index of Kabat.

In one embodiment, the hinge region of CH1 is modified such that the number of cysteine residues in the hinge region is altered, e.g., increased or decreased. This approach is described further in U.S. Pat. No. 5,677,425 by Bodmer et al. The number of cysteine residues in the hinge region of CH1 is altered to, for example, facilitate assembly of the light and heavy chains or to increase or decrease the stability of the antibody.

In another embodiment, the Fc hinge region of an antibody is mutated to decrease the biological half life of the antibody. More specifically, one or more amino acid mutations are introduced into the CH2-CH3 domain interface region of the Fc-hinge fragment such that the antibody has impaired Staphylococcal protein A (SpA) binding relative to native Fc-hinge domain SpA binding. This approach is described in further detail in U.S. Pat. No. 6,165,745 by Ward et al.

In another embodiment, the antibody is modified to increase its biological half life. Various approaches are possible. For example, one or more of the following mutations can be introduced: T252L, T254S, T256F, as described in U.S. Pat. No. 6,277,375 to Ward. Alternatively, to increase the biological half life, the antibody can be altered within the CH1 or CL region to contain a salvage receptor binding epitope taken from two loops of a CH2 domain of an Fc region of an IgG, as described in U.S. Pat. Nos. 5,869,046 and 6,121,022 by Presta et al.

In yet other embodiments, the Fc region is altered by replacing at least one amino acid residue with a different amino acid residue to alter the effector functions of the antibody. For example, one or more amino acids selected from amino acid residues 234, 235, 236, 237, 297, 318, 320 and 322 can be replaced with a different amino acid residue such that the antibody has an altered affinity for an effector ligand but retains the antigen-binding ability of the parent antibody. The effector ligand to which affinity is altered can be, for example, an Fc receptor or the C1 component of complement. This approach is described in further detail in U.S. Pat. Nos. 5,624,821 and 5,648,260, both by Winter et al.

In another example, one or more amino acids selected from amino acid residues 329, 331 and 322 can be replaced with a different amino acid residue such that the antibody has altered C1q binding and/or reduced or abolished complement dependent cytotoxicity (CDC). This approach is described in further detail in U.S. Pat. No. 6,194,551 by Idusogie et al.

In another example, one or more amino acid residues within amino acid positions 231 and 239 are altered to thereby alter the ability of the antibody to fix complement. This approach is described further in PCT Publication WO 94/29351 by Bodmer et al.

In yet another example, the Fc region is modified to increase the ability of the antibody to mediate antibody dependent cellular cytotoxicity (ADCC) and/or to increase the affinity of the antibody for an Fcγ receptor by modifying one or more amino acids at the following positions: 238, 239, 248, 249, 252, 255, 256, 258, 265, 267, 268, 269, 270, 272, 276, 278, 280, 283, 285, 286, 289, 290, 292, 293, 294, 295, 296, 298, 301, 303, 305, 307, 309, 312, 315, 320, 322, 324, 326, 327, 329, 330, 331, 333, 334, 335, 337, 338, 340, 360, 373, 376, 378, 382, 388, 389, 398, 414, 416, 419, 430,

434, 435, 437, 438 or 439. This approach is described further in PCT Publication WO 00/42072 by Presta. Moreover, the binding sites on human IgG1 for Fc gamma RI, Fc gamma RII, Fc gamma RIII and FcγRn have been mapped and variants with improved binding have been described (see Shields, R. L. et al. (2001) *J. Biol. Chem.* 276:6591-6604). Specific mutations at positions 256, 290, 298, 333, 334 and 339 are shown to improve binding to FcγRIII. Additionally, the following combination mutants are shown to improve Fcγma-RIII binding: T256A/S298A, S298A/E333A, S298A/K224A and S298A/E333A/K334A. Furthermore, mutations such as M252Y/S254T/T256E or M428L/N434S improve binding to FcγRn and increase antibody circulation half-life (see Chan C A and Carter P J (2010) *Nature Rev Immunol* 10:301-316).

In still another embodiment, the glycosylation of an antibody is modified. For example, an aglycosylated antibody can be made (i.e., the antibody lacks glycosylation). Glycosylation can be altered to, for example, increase the affinity of the antibody for antigen. Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. For example, one or more amino acid substitutions can be made that result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site. Such aglycosylation may increase the affinity of the antibody for antigen. Such an approach is described in further detail in U.S. Pat. Nos. 5,714,350 and 6,350,861 by Co et al.

Additionally or alternatively, an antibody can be made that has an altered type of glycosylation, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNAc structures. Such altered glycosylation patterns have been demonstrated to increase the ADCC ability of antibodies. Such carbohydrate modifications can be accomplished by, for example, expressing the antibody in a host cell with altered glycosylation machinery. Cells with altered glycosylation machinery have been described in the art and can be used as host cells in which to express recombinant antibodies according to at least some embodiments of the invention to thereby produce an antibody with altered glycosylation. For example, the cell lines Ms704, Ms705, and Ms709 lack the fucosyltransferase gene, FUT8 (alpha (1,6) fucosyltransferase), such that antibodies expressed in the Ms704, Ms705, and Ms709 cell lines lack fucose on their carbohydrates. The Ms704, Ms705, and Ms709 FUT8^{-/-} cell lines are created by the targeted disruption of the FUT8 gene in CHO/DG44 cells using two replacement vectors (see U.S. Patent Publication No. 20040110704 by Yamane et al. and Yamane-Ohnuki et al. (2004) *Biotechnol Bioeng* 87:614-22). As another example, EP 1,176,195 by Hanai et al. describes a cell line with a functionally disrupted FUT8 gene, which encodes a fucosyl transferase, such that antibodies expressed in such a cell line exhibit hypofucosylation by reducing or eliminating the alpha 1,6 bond-related enzyme. Hanai et al. also describe cell lines which have a low enzyme activity for adding fucose to the N-acetylglucosamine that binds to the Fc region of the antibody or does not have the enzyme activity, for example the rat myeloma cell line YB2/0 (ATCC CRL 1662). PCT Publication WO 03/035835 by Presta describes a variant CHO cell line, Lec13 cells, with reduced ability to attach fucose to Asn(297)-linked carbohydrates, also resulting in hypofucosylation of antibodies expressed in that host cell (see also Shields, R. L. et al. (2002) *J. Biol. Chem.* 277: 26733-26740). PCT Publication WO 99/54342 by Umana et al. describes cell lines engineered to express glycoprotein-modifying glycosyl transferases (e.g., beta(1,4)—N-acetyl-

glucosaminyltransferase III (GnTIII)) such that antibodies expressed in the engineered cell lines exhibit increased bisecting GlcNAc structures which results in increased ADCC activity of the antibodies (see also Umana et al. (1999) Nat. Biotech. 17:176-180). Alternatively, the fucose residues of the antibody may be cleaved off using a fucosidase enzyme. For example, the fucosidase α -L-fucosidase removes fucosyl residues from antibodies (Tarentino, A. L. et al. (1975) Biochem. 14:5516-23).

Another modification of the antibodies herein that is contemplated by the invention is pegylation. An antibody can be pegylated to, for example, increase the biological (e.g., serum) half life of the antibody. To pegylate an antibody, the antibody, or fragment thereof, typically is reacted with polyethylene glycol (PEG), such as a reactive ester or aldehyde derivative of PEG, under conditions in which one or more PEG groups become attached to the antibody or antibody fragment. Preferably, the pegylation is carried out via an acylation reaction or an alkylation reaction with a reactive PEG molecule (or an analogous reactive water-soluble polymer). As used herein, the term "polyethylene glycol" is intended to encompass any of the forms of PEG that have been used to derivatize other proteins, such as mono (C1-C10) alkoxy- or aryloxy-polyethylene glycol or polyethylene glycol-maleimide. In certain embodiments, the antibody to be pegylated is an aglycosylated antibody. Methods for pegylating proteins are known in the art and can be applied to the antibodies according to at least some embodiments of the invention. See for example, EP 0 154 316 by Nishimura et al. and EP 0 401 384 by Ishikawa et al.

Methods of Engineering Antibodies

As discussed above, anti-LY6G6F, anti-VSIG10, anti-TMEM25 or anti-LSR antibodies having VH and VK sequences disclosed herein can be used to create new anti-LY6G6F, anti-VSIG10, anti-TMEM25 or anti-LSR antibodies, respectively, by modifying the VH and/or VL sequences, or the constant regions attached thereto. Thus, in another aspect according to at least some embodiments of the invention, the structural features of an anti-LY6G6F, anti-VSIG10, anti-TMEM25 or anti-LSR antibody according to at least some embodiments of the invention, are used to create structurally related anti-LY6G6F, anti-VSIG10, anti-TMEM25 or anti-LSR antibodies that retain at least one functional property of the antibodies according to at least some embodiments of the invention, such as binding to human LY6G6F, VSIG10, TMEM25 or LSR, respectively. For example, one or more CDR regions of one LY6G6F, VSIG10, TMEM25 or LSR antibody or mutations thereof, can be combined recombinantly with known framework regions and/or other CDRs to create additional, recombinantly-engineered, anti-LY6G6F, anti-VSIG10, anti-TMEM25 or anti-LSR antibodies according to at least some embodiments of the invention, as discussed above. Other types of modifications include those described in the previous section. The starting material for the engineering method is one or more of the VH and/or VK sequences provided herein, or one or more CDR regions thereof. To create the engineered antibody, it is not necessary to actually prepare (i.e., express as a protein) an antibody having one or more of the VH and/or VK sequences provided herein, or one or more CDR regions thereof. Rather, the information contained in the sequences is used as the starting material to create a "second generation" sequences derived from the original sequences and then the "second generation" sequences is prepared and expressed as a protein.

Standard molecular biology techniques can be used to prepare and express altered antibody sequence.

Preferably, the antibody encoded by the altered antibody sequences is one that retains one, some or all of the functional properties of the anti-LY6G6F, anti-VSIG10, anti-TMEM25 or anti-LSR antibodies, respectively, produced by methods and with sequences provided herein, which functional properties include binding to LY6G6F, VSIG10, TMEM25 or LSR antigen with a specific KD level or less and/or modulating B7 costimulation and/or selectively binding to desired target cells such as for example melanoma, cancers of liver, renal, brain, breast, colon, lung, ovary, pancreas, prostate, stomach, multiple myeloma and hematopoietic cancer, including but not limited to lymphoma (Hodgkin's and non Hodgkin's), acute and chronic lymphoblastic leukemia and acute and chronic myeloid leukemia, that express LY6G6F, VSIG10, TMEM25 and/or LSR antigen.

The functional properties of the altered antibodies can be assessed using standard assays available in the art and/or described herein.

In certain embodiments of the methods of engineering antibodies according to at least some embodiments of the invention, mutations can be introduced randomly or selectively along all or part of an anti-LY6G6F, anti-VSIG10, anti-TMEM25 or anti-LSR antibody coding sequence and the resulting modified anti-LY6G6F, anti-VSIG10, anti-TMEM25 or anti-LSR antibodies can be screened for binding activity and/or other desired functional properties.

Mutational methods have been described in the art. For example, PCT Publication WO 02/092780 by Short describes methods for creating and screening antibody mutations using saturation mutagenesis, synthetic ligation assembly, or a combination thereof. Alternatively, PCT Publication WO 03/074679 by Lazar et al. describes methods of using computational screening methods to optimize physiochemical properties of antibodies.

Nucleic Acid Molecules Encoding Antibodies

Another aspect of the invention pertains to nucleic acid molecules that encode the antibodies according to at least some embodiments of the invention. The nucleic acids may be present in whole cells, in a cell lysate, or in a partially purified or substantially pure form. A nucleic acid is "isolated" or "rendered substantially pure" when purified away from other cellular components or other contaminants, e.g., other cellular nucleic acids or proteins, by standard techniques, including alkaline/SDS treatment, CsCl banding, column chromatography, agarose gel electrophoresis and others well known in the art. See, F. Ausubel, et al., ed. (1987) Current Protocols in Molecular Biology, Greene Publishing and Wiley Interscience, New York. A nucleic acid according to at least some embodiments of the invention can be, for example, DNA or RNA and may or may not contain intronic sequences. In a preferred embodiment, the nucleic acid is a cDNA molecule.

Nucleic acids according to at least some embodiments of the invention can be obtained using standard molecular biology techniques. For antibodies expressed by hybridomas (e.g., hybridomas prepared from transgenic mice carrying human immunoglobulin genes as described further below), cDNAs encoding the light and heavy chains of the antibody made by the hybridoma can be obtained by standard PCR amplification or cDNA cloning techniques. For antibodies obtained from an immunoglobulin gene library (e.g., using phage display techniques), nucleic acid encoding the antibody can be recovered from the library.

Once DNA fragments encoding VH and VL segments are obtained, these DNA fragments can be further manipulated by standard recombinant DNA techniques, for example to convert the variable region genes to full-length antibody

chain genes, to Fab fragment genes or to a scFv gene. In these manipulations, a VL- or VH-encoding DNA fragment is operatively linked to another DNA fragment encoding another protein, such as an antibody constant region or a flexible linker.

The term "operatively linked", as used in this context, is intended to mean that the two DNA fragments are joined such that the amino acid sequences encoded by the two DNA fragments remain in-frame.

The isolated DNA encoding the VH region can be converted to a full-length heavy chain gene by operatively linking the VH-encoding DNA to another DNA molecule encoding heavy chain constant regions (CH1, CH2 and CH3). The sequences of human heavy chain constant region genes are known in the art (see e.g., Kabat, E. A., et al. (1991) *Sequences of Proteins of Immunological Interest*, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242) and DNA fragments encompassing these regions can be obtained by standard PCR amplification. The heavy chain constant region can be an IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgM or IgD constant region, but most preferably is an IgG1 or IgG4 constant region. For a Fab fragment heavy chain gene, the VH-encoding DNA can be operatively linked to another DNA molecule encoding only the heavy chain CH1 constant region.

The isolated DNA encoding the VL region can be converted to a full-length light chain gene (as well as a Fab light chain gene) by operatively linking the VL-encoding DNA to another DNA molecule encoding the light chain constant region, CL. The sequences of human light chain constant region genes are known in the art (see e.g., Kabat, E. A., et al. (1991) *Sequences of Proteins of Immunological Interest*, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242) and DNA fragments encompassing these regions can be obtained by standard PCR amplification. The light chain constant region can be a kappa or lambda constant region, but most preferably is a kappa constant region.

To create a scFv gene, the VH- and VL-encoding DNA fragments are operatively linked to another fragment encoding a flexible linker, e.g., encoding the amino acid sequence (Gly4-Ser)3, such that the VH and VL sequences can be expressed as a contiguous single-chain protein, with the VL and VH regions joined by the flexible linker (see e.g., Bird et al. (1988) *Science* 242:423-426; Huston et al. (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883; McCafferty et al., (1990) *Nature* 348:552-554).

Production of Anti-LY6G6F, Anti-VSIG10, Anti-TMEM25 or Anti-LSR Monoclonal Antibodies

Monoclonal antibodies (mAbs) of the present invention can be produced by a variety of techniques, including conventional monoclonal antibody methodology e.g., the standard somatic cell hybridization technique of Kohler and Milstein (1975) *Nature* 256:495. Although somatic cell hybridization procedures are preferred, in principle, other techniques for producing monoclonal antibody can be employed e.g., viral or oncogenic transformation of B lymphocytes.

A preferred animal system for preparing hybridomas is the murine system. Hybridoma production in the mouse is a very well-established procedure. Immunization protocols and techniques for isolation of immunized splenocytes for fusion are known in the art. Fusion partners (e.g., murine myeloma cells) and fusion procedures are also known.

Chimeric or humanized antibodies of the present invention can be prepared based on the sequence of a murine monoclonal antibody prepared as described above. DNA encoding

the heavy and light chain immunoglobulins can be obtained from the murine hybridoma of interest and engineered to contain non-murine (e.g., human) immunoglobulin sequences using standard molecular biology techniques. For example, to create a chimeric antibody, the murine variable regions can be linked to human constant regions using methods known in the art (see e.g., U.S. Pat. No. 4,816,567 to Cabilly et al.). To create a humanized antibody, the murine CDR regions can be inserted into a human framework using methods known in the art (see e.g., U.S. Pat. No. 5,225,539 to Winter, and U.S. Pat. Nos. 5,530,101; 5,585,089; 5,693,762 and 6,180,370 to Queen et al.).

According to at least some embodiments of the invention, the antibodies are human monoclonal antibodies. Such human monoclonal antibodies directed against LY6G6F, VSIG10, TMEM25 and/or LSR can be generated using transgenic or transchromosomal mice carrying parts of the human immune system rather than the mouse system. These transgenic and transchromosomal mice include mice referred to herein as the HuMAb Mouse™ and KM Mouse™, respectively, and are collectively referred to herein as "human Ig mice." The HuMAb Mouse™ (Medarex, Inc.) contains human immunoglobulin gene miniloci that encode unrearranged human heavy (.mu. and .gamma.) and .kappa. light chain immunoglobulin sequences, together with targeted mutations that inactivate the endogenous .mu. and .kappa. chain loci (see e.g., Lonberg, et al. (1994) *Nature* 368(6474): 856-859). Accordingly, the mice exhibit reduced expression of mouse IgM or .kappa., and in response to immunization, the introduced human heavy and light chain transgenes undergo class switching and somatic mutation to generate high affinity human IgGkappa. monoclonal (Lonberg, N. et al. (1994), *supra*; reviewed in Lonberg, N. (1994) *Handbook of Experimental Pharmacology* 113:49-101; Lonberg, N. and Huszar, D. (1995) *Intern. Rev. Immunol.* 13: 65-93, and Harding, F. and Lonberg, N. (1995) *Ann N.Y. Acad. Sci.* 764:536-546). The preparation and use of the HuMAb Mouse®, and the genomic modifications carried by such mice, is further described in Taylor, L. et al. (1992) *Nucleic Acids Research* 20:6287-6295; Chen, J. et al. (1993) *International Immunology* 5:647-656; Tuaille et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:3720-3724; Choi et al. (1993) *Nature Genetics* 4:117-123; Chen, J. et al. (1993) *EMBO J.* 12: 821-830; Tuaille et al. (1994) *J. Immunol.* 152:2912-2920; Taylor, L. et al. (1994) *International Immunology* 6:579-591; and Fishwild, D. et al. (1996) *Nature Biotechnology* 14: 845-851, the contents of all of which are hereby specifically incorporated by reference in their entirety. See further, U.S. Pat. Nos. 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,789,650; 5,877,397; 5,661,016; 5,814,318; 5,874,299; and 5,770,429; all to Lonberg and Kay; U.S. Pat. No. 5,545,807 to Surani et al.; PCT Publication Nos. WO 92/03918, WO 93/12227, WO 94/25585, WO 97/13852, WO 98/24884 and WO 99/45962, all to Lonberg and Kay; and PCT Publication No. WO 01/14424 to Korman et al.

In another embodiment, human antibodies according to at least some embodiments of the invention can be raised using a mouse that carries human immunoglobulin sequences on transgenes and transchromosomes, such as a mouse that carries a human heavy chain transgene and a human light chain transchromosome. Such mice, referred to herein as "KM Mice™", are described in detail in PCT Publication WO 02/43478 to Ishida et al.

Still further, alternative transgenic animal systems expressing human immunoglobulin genes are available in the art and can be used to raise anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR antibodies according to at least

some embodiments of the invention. For example, an alternative transgenic system referred to as the Xenomouse (Abgenix, Inc.) can be used; such mice are described in, for example, U.S. Pat. Nos. 5,939,598; 6,075,181; 6,114,598; 6,150,584 and 6,162,963 to Kucherlapati et al.

Moreover, alternative transchromosomal animal systems expressing human immunoglobulin genes are available in the art and can be used to raise anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR antibodies according to at least some embodiments of the invention. For example, mice carrying both a human heavy chain transchromosome and a human light chain transchromosome, referred to as "TC mice" can be used; such mice are described in Tomizuka et al. (2000) Proc. Natl. Acad. Sci. USA 97:722-727. Furthermore, cows carrying human heavy and light chain transchromosomes have been described in the art (Kuroiwa et al. (2002) Nature Biotechnology 20:889-894) and can be used to raise anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR antibodies according to at least some embodiments of the invention.

Human monoclonal antibodies according to at least some embodiments of the invention can also be prepared using phage display methods for screening libraries of human immunoglobulin genes. Such phage display methods for isolating human antibodies are established in the art. See for example: U.S. Pat. Nos. 5,223,409; 5,403,484; and 5,571,698 to Ladner et al.; U.S. Pat. Nos. 5,427,908 and 5,580,717 to Dower et al.; U.S. Pat. Nos. 5,969,108 and 6,172,197 to McCafferty et al.; and U.S. Pat. Nos. 5,885,793; 6,521,404; 6,544,731; 6,555,313; 6,582,915 and 6,593,081 to Griffiths et al.

Human monoclonal antibodies according to at least some embodiments of the invention can also be prepared using SCID mice into which human immune cells have been reconstituted such that a human antibody response can be generated upon immunization. Such mice are described in, for example, U.S. Pat. Nos. 5,476,996 and 5,698,767 to Wilson et al.

Immunization of Human Ig Mice

When human Ig mice are used to raise human antibodies according to at least some embodiments of the invention, such mice can be immunized with a purified or enriched preparation of LY6G6F, VSIG10, TMEM25 and/or LSR antigen and/or recombinant LY6G6F, VSIG10, TMEM25 and/or LSR, or LY6G6F, VSIG10, TMEM25 and/or LSR fusion protein, as described by Lonberg, N. et al. (1994) Nature 368(6474): 856-859; Fishwild, D. et al. (1996) Nature Biotechnology 14: 845-851; and PCT Publication WO 98/24884 and WO 01/14424. Preferably, the mice will be 6-16 weeks of age upon the first infusion. For example, a purified or recombinant preparation (5-50 μ g) of LY6G6F, VSIG10, TMEM25 and/or LSR antigen can be used to immunize the human Ig mice intraperitoneally.

Prior experience with various antigens by others has shown that the transgenic mice respond when initially immunized intraperitoneally (IP) with antigen in complete Freund's adjuvant, followed by every other week IP immunizations (up to a total of 6) with antigen in incomplete Freund's adjuvant. However, adjuvants other than Freund's are also found to be effective. In addition, whole cells in the absence of adjuvant are found to be highly immunogenic. The immune response can be monitored over the course of the immunization protocol with plasma samples being obtained by retroorbital bleeds. The plasma can be screened by ELISA (as described below), and mice with sufficient titers of anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR human immunoglobulin can be used for fusions. Mice can be boosted intra-

venously with antigen 3 days before sacrifice and removal of the spleen. It is expected that 2-3 fusions for each immunization may need to be performed. Between 6 and 24 mice are typically immunized for each antigen. Usually both HCo7 and HCo12 strains are used. In addition, both HCo7 and HCo12 transgene can be bred together into a single mouse having two different human heavy chain transgenes (HCo7/HCo12). Alternatively or additionally, the KM Mouse® strain can be used.

Generation of Hybridomas Producing Human Monoclonal Antibodies

To generate hybridomas producing human monoclonal antibodies according to at least some embodiments of the invention, splenocytes and/or lymph node cells from immunized mice can be isolated and fused to an appropriate immortalized cell line, such as a mouse myeloma cell line. The resulting hybridomas can be screened for the production of antigen-specific antibodies. For example, single cell suspensions of splenic lymphocytes from immunized mice can be fused to one-sixth the number of P3 \times 63-Ag8.653 nonsecreting mouse myeloma cells (ATCC, CRL 1580) with 50% PEG. Cells are plated at approximately 2 \times 10⁵ in flat bottom microtiter plate, followed by a two week incubation in selective medium containing 20% fetal Clone Serum, 18% "653" conditioned media, 5% origen (IGEN), 4 mM L-glutamine, 1 mM sodium pyruvate, 5 mM HEPES, 0.055 mM 2-mercaptoethanol, 50 units/ml penicillin, 50 mg/ml streptomycin, 50 mg/ml gentamycin and 1 \times HAT (Sigma; the HAT is added 24 hours after the fusion). After approximately two weeks, cells can be cultured in medium in which the HAT is replaced with HT. Individual wells can then be screened by ELISA for human monoclonal IgM and IgG antibodies. Once extensive hybridoma growth occurs, medium can be observed usually after 10-14 days. The antibody secreting hybridomas can be replated, screened again, and if still positive for human IgG, the monoclonal antibodies can be subcloned at least twice by limiting dilution. The stable subclones can then be cultured in vitro to generate small amounts of antibody in tissue culture medium for characterization.

To purify human monoclonal antibodies, selected hybridomas can be grown in two-liter spinner-flasks for monoclonal antibody purification. Supernatants can be filtered and concentrated before affinity chromatography with protein A-Sepharose (Pharmacia, Piscataway, N.J.). Eluted IgG can be checked by gel electrophoresis and high performance liquid chromatography to ensure purity. The buffer solution can be exchanged into PBS, and the concentration can be determined by OD280 using 1.43 extinction coefficient. The monoclonal antibodies can be aliquoted and stored at -80 degrees C.

Generation of Transfectomas Producing Monoclonal Antibodies

Antibodies according to at least some embodiments of the invention also can be produced in a host cell transfectoma using, for example, a combination of recombinant DNA techniques and gene transfection methods as is well known in the art (e.g., Morrison, S. (1985) Science 229:1202).

For example, to express the antibodies, or antibody fragments thereof, DNAs encoding partial or full-length light and heavy chains, can be obtained by standard molecular biology techniques (e.g., PCR amplification or cDNA cloning using a hybridoma that expresses the antibody of interest) and the DNAs can be inserted into expression vectors such that the genes are operatively linked to transcriptional and translational control sequences. In this context, the term "operatively linked" is intended to mean that an antibody gene is

ligated into a vector such that transcriptional and translational control sequences within the vector serve their intended function of regulating the transcription and translation of the antibody gene. The expression vector and expression control sequences are chosen to be compatible with the expression host cell used. The antibody light chain gene and the antibody heavy chain gene can be inserted into separate vector or, more typically, both genes are inserted into the same expression vector. The antibody genes are inserted into the expression vector by standard methods (e.g., ligation of complementary restriction sites on the antibody gene fragment and vector, or blunt end ligation if no restriction sites are present). The light and heavy chain variable regions of the antibodies described herein can be used to create full-length antibody genes of any antibody isotype by inserting them into expression vectors already encoding heavy chain constant and light chain constant regions of the desired isotype such that the VH segment is operatively linked to the CH segments within the vector and the VK segment is operatively linked to the CL segment within the vector. Additionally or alternatively, the recombinant expression vector can encode a signal peptide that facilitates secretion of the antibody chain from a host cell. The antibody chain gene can be cloned into the vector such that the signal peptide is linked in-frame to the amino terminus of the antibody chain gene. The signal peptide can be an immunoglobulin signal peptide or a heterologous signal peptide (i.e., a signal peptide from a non-immunoglobulin protein).

In addition to the antibody chain genes, the recombinant expression vectors according to at least some embodiments of the invention carry regulatory sequences that control the expression of the antibody chain genes in a host cell. The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (e.g., polyadenylation signals) that control the transcription or translation of the antibody chain genes. Such regulatory sequences are described, for example, in Goeddel (Gene Expression Technology, Methods in Enzymology 185, Academic Press, San Diego, Calif. (1990)). It will be appreciated by those skilled in the art that the design of the expression vector, including the selection of regulatory sequences, may depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. Preferred regulatory sequences for mammalian host cell expression include viral elements that direct high levels of protein expression in mammalian cells, such as promoters and/or enhancers derived from cytomegalovirus (CMV), Simian Virus 40 (SV40), adenovirus, (e.g., the adenovirus major late promoter (AdMLP) and polyoma. Alternatively, nonviral regulatory sequences may be used, such as the ubiquitin promoter or .beta.-globin promoter. Still further, regulatory elements composed of sequences from different sources, such as the SR alpha. promoter system, which contains sequences from the SV40 early promoter and the long terminal repeat of human T cell leukemia virus type 1 (Takebe, Y. et al. (1988) Mol. Cell. Biol. 8:466-472).

In addition to the antibody chain genes and regulatory sequences, the recombinant expression vectors according to at least some embodiments of the invention may carry additional sequences, such as sequences that regulate replication of the vector in host cells (e.g., origins of replication) and selectable marker genes. The selectable marker gene facilitates selection of host cells into which the vector has been introduced (see, e.g., U.S. Pat. Nos. 4,399,216, 4,634,665 and 5,179,017, all by Axel et al.). For example, typically the selectable marker gene confers resistance to drugs, such as G418, hygromycin or methotrexate, on a host cell into which the vector has been introduced. Preferred selectable marker

genes include the dihydrofolate reductase (DHFR) gene (for use in dhfr-host cells with methotrexate selection/amplification) and the neo gene (for G418 selection).

For expression of the light and heavy chains, the expression vectors encoding the heavy and light chains is transfected into a host cell by standard techniques. The various forms of the term "transfection" are intended to encompass a wide variety of techniques commonly used for the introduction of exogenous DNA into a prokaryotic or eukaryotic host cell, e.g., electroporation, calcium-phosphate precipitation, DEAE-dextran transfection and the like. Although it is theoretically possible to express the antibodies according to at least some embodiments of the invention in either prokaryotic or eukaryotic host cells, expression of antibodies in eukaryotic cells, and most preferably mammalian host cells, is the most preferred because such eukaryotic cells, and in particular mammalian cells, are more likely than prokaryotic cells to assemble and secrete a properly folded and immunologically active antibody. Prokaryotic expression of antibody genes has been reported to be ineffective for production of high yields of active antibody (Boss, M. A. and Wood, C. R. (1985) Immunology Today 6:12-13).

Preferred mammalian host cells for expressing the recombinant antibodies according to at least some embodiments of the invention include Chinese Hamster Ovary (CHO cells) (including dhfr-CHO cells, described in Urlaub and ChasM, (1980) Proc. Natl. Acad. Sci. USA 77:4216-4220, used with a DHFR selectable marker, e.g., as described in R. J. Kaufman and P. A. Sharp (1982) Mol. Biol. 159:601-621), NSO myeloma cells, COS cells and SP2 cells. In particular, for use with NSO myeloma cells, another preferred expression system is the GS gene expression system disclosed in WO 87/04462, WO 89/01036 and EP 338,841. When recombinant expression vectors encoding antibody genes are introduced into mammalian host cells, the antibodies are produced by culturing the host cells for a period of time sufficient to allow for expression of the antibody in the host cells or, more preferably, secretion of the antibody into the culture medium in which the host cells are grown. Antibodies can be recovered from the culture medium using standard protein purification methods.

Characterization of Antibody Binding to Antigen

Antibodies according to at least some embodiments of the invention can be tested for binding to LY6G6F, VSIG10, TMEM25 and/or LSR by, for example, standard ELISA. Briefly, microtiter plates are coated with purified LY6G6F, VSIG10, TMEM25 and/or LSR at 0.25 .mu.g/ml in PBS, and then blocked with 5% bovine serum albumin in PBS. Dilutions of antibody (e.g., dilutions of plasma from-immunized mice) are added to each well and incubated for 1-2 hours at 37 degrees C. The plates are washed with PBS/Tween and then incubated with secondary reagent (e.g., for human antibodies, a goat-anti-human IgG Fc-specific polyclonal reagent) conjugated to alkaline phosphatase for 1 hour at 37 degrees C. After washing, the plates are developed with pNPP substrate (1 mg/ml), and analyzed at OD of 405-650. Preferably, mice which develop the highest titers will be used for fusions.

An ELISA assay as described above can also be used to screen for hybridomas that show positive reactivity with LY6G6F, VSIG10, TMEM25 and/or LSR immunogen. Hybridomas that bind with high avidity to LY6G6F, VSIG10, TMEM25 and/or LSR are subcloned and further characterized. One clone from each hybridoma, which retains the reactivity of the parent cells (by ELISA), can be chosen for making a 5-10 vial cell bank stored at -140 degrees C., and for antibody purification.

To purify anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR antibodies, selected hybridomas can be grown in two-liter spinner-flasks for monoclonal antibody purification. Supernatants can be filtered and concentrated before affinity chromatography with protein A-sepharose (Pharmacia, Piscataway, N.J.). Eluted IgG can be checked by gel electrophoresis and high performance liquid chromatography to ensure purity. The buffer solution can be exchanged into PBS, and the concentration can be determined by OD280 using 1.43 extinction coefficient. The monoclonal antibodies can be aliquoted and stored at -80 degrees C.

To determine if the selected anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR monoclonal antibodies bind to unique epitopes, each antibody can be biotinylated using commercially available reagents (Pierce, Rockford, Ill.). Competition studies using unlabeled monoclonal antibodies and biotinylated monoclonal antibodies can be performed using LY6G6F, VSIG10, TMEM25 and/or LSR coated-ELISA plates as described above. Biotinylated mAb binding can be detected with a strep-avidin-alkaline phosphatase probe.

To determine the isotype of purified antibodies, isotype ELISAs can be performed using reagents specific for antibodies of a particular isotype. For example, to determine the isotype of a human monoclonal antibody, wells of microtiter plates can be coated with 1 .mu.g/ml of anti-human immunoglobulin overnight at 4 degrees C. After blocking with 1% BSA, the plates are reacted with 1 mug/ml or less of test monoclonal antibodies or purified isotype controls, at ambient temperature for one to two hours. The wells can then be reacted with either human IgG1 or human IgM-specific alkaline phosphatase-conjugated probes. Plates are developed and analyzed as described above.

Anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR human IgGs can be further tested for reactivity with LY6G6F, VSIG10, TMEM25 and/or LSR antigen, respectively, by Western blotting. Briefly, LY6G6F, VSIG10, TMEM25 and/or LSR antigen can be prepared and subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis. After electrophoresis, the separated antigens are transferred to nitrocellulose membranes, blocked with 10% fetal calf serum, and probed with the monoclonal antibodies to be tested. Human IgG binding can be detected using anti-human IgG alkaline phosphatase and developed with BCIP/NBT substrate tablets (Sigma Chem. Co., St. Louis, Mo.).

Alternative Scaffolds

According to at least some embodiments the invention relates to protein scaffolds with specificities and affinities in a range similar to specific antibodies. According to at least some embodiments the present invention relates to an antigen-binding construct comprising a protein scaffold which is linked to one or more epitope-binding domains. Such engineered protein scaffolds are usually obtained by designing a random library with mutagenesis focused at a loop region or at an otherwise permissible surface area and by selection of variants against a given target via phage display or related techniques. According to at least some embodiments the invention relates to alternative scaffolds including, but not limited to, anticalins, DARPin, Armadillo repeat proteins, protein A, lipocalins, fibronectin domain, ankyrin consensus repeat domain, thioredoxin, chemically constrained peptides and the like. According to at least some embodiments the invention relates to alternative scaffolds that are used as therapeutic agents for treatment of cancer, autoimmune and infectious diseases as well as for in vivo diagnostics.

According to at least some embodiments the invention further provides a pharmaceutical composition comprising an antigen binding construct as described herein a pharmaceutically acceptable carrier.

The term 'Protein Scaffold' as used herein includes but is not limited to an immunoglobulin (Ig) scaffold, for example an IgG scaffold, which may be a four chain or two chain antibody, or which may comprise only the Fc region of an antibody, or which may comprise one or more constant regions from an antibody, which constant regions may be of human or primate origin, or which may be an artificial chimera of human and primate constant regions. Such protein scaffolds may comprise antigen-binding sites in addition to the one or more constant regions, for example where the protein scaffold comprises a full IgG. Such protein scaffolds will be capable of being linked to other protein domains, for example protein domains which have antigen-binding sites, for example epitope-binding domains or ScFv domains.

A "domain" is a folded protein structure which has tertiary structure independent of the rest of the protein. Generally, domains are responsible for discrete functional properties of proteins and in many cases may be added, removed or transferred to other proteins without loss of function of the remainder of the protein and/or of the domain. A "single antibody variable domain" is a folded polypeptide domain comprising sequences characteristic of antibody variable domains. It therefore includes complete antibody variable domains and modified variable domains, for example, in which one or more loops have been replaced by sequences which are not characteristic of antibody variable domains, or antibody variable domains which have been truncated or comprise N- or C-terminal extensions, as well as folded fragments of variable domains which retain at least the binding activity and specificity of the full-length domain.

The phrase "immunoglobulin single variable domain" refers to an antibody variable domain (VH, V H₁, V L) that specifically binds an antigen or epitope independently of a different V region or domain. An immunoglobulin single variable domain can be present in a format (e.g., homo- or hetero-multimer) with other, different variable regions or variable domains where the other regions or domains are not required for antigen binding by the single immunoglobulin variable domain (i.e., where the immunoglobulin single variable domain binds antigen independently of the additional variable domains). A "domain antibody" or "dAb" is the same as an "immunoglobulin single variable domain" which is capable of binding to an antigen as the term is used herein. An immunoglobulin single variable domain may be a human antibody variable domain, but also includes single antibody variable domains from other species such as rodent (for example, as disclosed in WO 00/29004), nurse shark and Camelid V HH dAbs. Camelid V HH are immunoglobulin single variable domain polypeptides that are derived from species including camel, llama, alpaca, dromedary, and guanaco, which produce heavy chain antibodies naturally devoid of light chains. Such V HH domains may be humanised according to standard techniques available in the art, and such domains are still considered to be "domain antibodies" according to the invention. As used herein "VH includes camelid V HH domains. NARV are another type of immunoglobulin single variable domain which were identified in cartilaginous fish including the nurse shark. These domains are also known as Novel Antigen Receptor variable region (commonly abbreviated to V(NAR) or NARV). For further details see Mol. Immunol. 44, 656-665 (2006) and US20050043519A.

The term "epitope-binding domain" refers to a domain that specifically binds an antigen or epitope independently of a different V region or domain, this may be a domain antibody (dAb), for example a human, camelid or shark immunoglobulin single variable domain or it may be a domain which is a derivative of a scaffold selected from the group consisting of CTLA-4 (Evibody); lipocalin; Protein A derived molecules such as Z-domain of Protein A (Affibody, SpA), A-domain (Avimer/Maxibody); Heat shock proteins such as GroEl and GroES; transferrin (trans-body); ankyrin repeat protein (DARPin); peptide aptamer; C-type lectin domain (Tetranectin); human γ -crystallin and human ubiquitin (affilins); PDZ domains; scorpion toxin/kunitz type domains of human protease inhibitors; Armadillo repeat proteins, thioredoxin, and fibronectin (adnectin); which has been subjected to protein engineering in order to obtain binding to a ligand other than the natural ligand.

Loops corresponding to CDRs of antibodies can be substituted with heterologous sequence to confer different binding properties i.e. Evi-bodies. For further details see Journal of Immunological Methods 248 (1-2), 31-45 (2001) Lipocalins are a family of extracellular proteins which transport small hydrophobic molecules such as steroids, bilins, retinoids and lipids. They have a rigid secondary structure with a number of loops at the open end of the conical structure which can be engineered to bind to different target antigens. Anticalins are between 160-180 amino acids in size, and are derived from lipocalins. For further details see Biochim Biophys Acta 1482: 337-350 (2000), U.S. Pat. No. 7,250,297B1 and US20070224633. An affibody is a scaffold derived from Protein A of *Staphylococcus aureus* which can be engineered to bind to antigen. The domain consists of a three-helical bundle of approximately 58 amino acids. Libraries have been generated by randomisation of surface residues. For further details see Protein Eng. Des. Sel. 17, 455-462 (2004) and EP1641818A1 Avimers are multidomain proteins derived from the A-domain scaffold family. The native domains of approximately 35 amino acids adopt a defined disulphide bonded structure. Diversity is generated by shuffling of the natural variation exhibited by the family of A-domains. For further details see Nature Biotechnology 23(12), 1556-1561 (2005) and Expert Opinion on Investigational Drugs 16(6), 909-917 (June 2007) A transferrin is a monomeric serum transport glycoprotein. Transferrins can be engineered to bind different target antigens by insertion of peptide sequences in a permissive surface loop. Examples of engineered transferrin scaffolds include the Trans-body. For further details see J. Biol. Chem. 274, 24066-24073 (1999).

Designed Ankyrin Repeat Proteins (DARPs) are derived from Ankyrin which is a family of proteins that mediate attachment of integral membrane proteins to the cytoskeleton. A single ankyrin repeat is a 33 residue motif consisting of two α helices; β -turn. They can be engineered to bind different target antigens by randomising residues in the first α -helix and a β -turn of each repeat. Their binding interface can be increased by increasing the number of modules (a method of affinity maturation). For further details see J. Mol. Biol. 332, 489-503 (2003), PNAS 100(4), 1700-1705 (2003) and J. Mol. Biol. 369, 1015-1028 (2007) and US20040132028A1.

Fibronectin is a scaffold which can be engineered to bind to antigen. Adnectins consists of a backbone of the natural amino acid sequence of the 10th domain of the 15 repeating units of human fibronectin type III (FN3). Three loops at one end of the β ; sandwich can be engineered to enable an Adnectin to specifically recognize a therapeutic target of

interest. For further details see Protein Eng. Des. Sel. 18, 435-444 (2005), US200801 39791, WO2005056764 and U.S. Pat. No. 6,818,418B1.

Peptide aptamers are combinatorial recognition molecules that consist of a constant scaffold protein, typically thioredoxin (TrxA) which contains a constrained variable peptide loop inserted at the active site. For further details see Expert Opin. Biol. Ther. 5, 783-797 (2005).

Microbodies are derived from naturally occurring microproteins of 25-50 amino acids in length which contain 3-4 cysteine bridges—examples of microproteins include KalataB1 and conotoxin and knottins. The microproteins have a loop which can be engineered to include up to 25 amino acids without affecting the overall fold of the microprotein. For further details of engineered knottin domains, see WO2008098796.

Other epitope binding domains include proteins which have been used as a scaffold to engineer different target antigen binding properties include human γ beta-crystallin and human ubiquitin (affilins), kunitz type domains of human protease inhibitors, PDZ-domains of the Ras-binding protein AF-6, scorpion toxins (charybdotoxin), C-type lectin domain (tetranectins) are reviewed in Chapter 7-Non-Antibody Scaffolds from Handbook of Therapeutic Antibodies (2007, edited by Stefan Dubel) and Protein Science 15:14-27 (2006). Epitope binding domains of the present invention could be derived from any of these alternative protein domains.

Conjugates or Immunoconjugates

The present invention encompasses conjugates for use in immune therapy comprising the LY6G6F, VSIG10, TMEM25 and/or LSR antigen and soluble portions thereof including the ectodomain or portions or variants thereof. For example the invention encompasses conjugates wherein the ECD of the LY6G6F, VSIG10, TMEM25 and/or LSR antigen is attached to an immunoglobulin or fragment thereof. The invention contemplates the use thereof for promoting or inhibiting LY6G6F, VSIG10, TMEM25 and/or LSR antigen activities such as immune costimulation and the use thereof in treating transplant, autoimmune, and cancer indications described herein.

In another aspect, the present invention features antibody-drug conjugates (ADCs), used for example for treatment of cancer, consisting of an antibody (or antibody fragment such as a single-chain variable fragment [scFv]) linked to a payload drug (often cytotoxic). The antibody causes the ADC to bind to the target cancer cells. Often the ADC is then internalized by the cell and the drug is released into the cell. Because of the targeting, the side effects are lower and give a wider therapeutic window. Hydrophilic linkers (e.g., PEG4Ma1) help prevent the drug being pumped out of resistant cancer cells through MDR (multiple drug resistance) transporters. ADCs based on cleavable linkers are thought to have a less favorable therapeutic window, but targets (tumor cell surface antigens) that do not get internalized efficiently seem more suitable for cleavable linkers.

In another aspect, the present invention features immunoconjugates comprising an anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR antibody, or a fragment thereof, conjugated to a therapeutic moiety, such as a cytotoxin, a drug (e.g., an immunosuppressant) or a radiotoxin. Such conjugates are referred to herein as "immunoconjugates" Immunoconjugates that include one or more cytotoxins are referred to as "immunotoxins." A cytotoxin or cytotoxic agent includes any agent that is detrimental to (e.g., kills) cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunomycin, and other cytotoxic agents.

rubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents also include, for example, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

Other preferred examples of therapeutic cytotoxins that can be conjugated to an antibody according to at least some embodiments of the invention include duocarmycins, calicheamicins, maytansines and auristatins, and derivatives thereof. An example of a calicheamicin antibody conjugate is commercially available (Mylotarg™; Wyeth).

Cytotoxins can be conjugated to antibodies according to at least some embodiments of the invention using linker technology available in the art. Examples of linker types that have been used to conjugate a cytotoxin to an antibody include, but are not limited to, hydrazones, thioethers, esters, disulfides and peptide-containing linkers. A linker can be chosen that is, for example, susceptible to cleavage by low pH within the lysosomal compartment or susceptible to cleavage by proteases, such as proteases preferentially expressed in tumor tissue such as cathepsins (e.g., cathepsins B, C, D).

For further discussion of types of cytotoxins, linkers and methods for conjugating therapeutic agents to antibodies, see also Saito, G. et al. (2003) *Adv. Drug Deliv. Rev.* 55:199-215; Trail, P. A. et al. (2003) *Cancer Immunol. Immunother.* 52:328-337; Payne, G. (2003) *Cancer Cell* 3:207-212; Allen, T. M. (2002) *Nat. Rev. Cancer* 2:750-763; Pastan, I. and Kreitman, R. J. (2002) *Curr. Opin. Investig. Drugs* 3:1089-1091; Senter, P. D. and Springer, C. J. (2001) *Adv. Drug Deliv. Rev.* 53:247-264.

Antibodies of the present invention also can be conjugated to a radioactive isotope to generate cytotoxic radiopharmaceuticals, also referred to as radioimmunoconjugates. Examples of radioactive isotopes that can be conjugated to antibodies for use diagnostically or therapeutically include, but are not limited to, iodine 131, indium 111, yttrium 90 and lutetium 177. Methods for preparing radioimmunoconjugates are established in the art. Examples of radioimmunoconjugates are commercially available, including Zevalin (IDEC Pharmaceuticals) and Bexxar. (Corixa Pharmaceuticals), and similar methods can be used to prepare radioimmunoconjugates using the antibodies according to at least some embodiments of the invention.

The antibody conjugates according to at least some embodiments of the invention can be used to modify a given biological response, and the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, an enzymatically active toxin, or active fragment thereof, such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor or interferon- γ ; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulo-

cyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Amon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.*, 62:119-58 (1982).

Bispecific Molecules

In another aspect, the present invention features bispecific molecules comprising an anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR antibody, or a fragment thereof, according to at least some embodiments of the invention. An antibody according to at least some embodiments of the invention, or antigen-binding portions thereof, can be derivatized or linked to another functional molecule, e.g., another peptide or protein (e.g., another antibody or ligand for a receptor) to generate a bispecific molecule that binds to at least two different binding sites or target molecules. The antibody according to at least some embodiments of the invention may in fact be derivatized or linked to more than one other functional molecule to generate multispecific molecules that bind to more than two different binding sites and/or target molecules; such multispecific molecules are also intended to be encompassed by the term "bispecific molecule" as used herein. To create a bispecific molecule according to at least some embodiments of the invention, an antibody can be functionally linked (e.g., by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other binding molecules, such as another antibody, antibody fragment, peptide or binding mimetic, such that a bispecific molecule results.

Accordingly, the present invention includes bispecific molecules comprising at least one first binding specificity for LY6G6F, VSIG10, TMEM25 and/or LSR and a second binding specificity for a second target epitope. According to at least some embodiments of the invention, the second target epitope is an Fc receptor, e.g., human Fc gamma RI (CD64) or a human Fc alpha receptor (CD89). Therefore, the invention includes bispecific molecules capable of binding both to Fc gamma. R, Fc alpha R or Fc epsilon R expressing effector cells (e.g., monocytes, macrophages or polymorphonuclear cells (PMNs)), and to target cells expressing LY6G6F, VSIG10, TMEM25 and/or LSR, respectively. These bispecific molecules target LY6G6F, VSIG10, TMEM25 and/or LSR expressing cells to effector cell and trigger Fc receptor-mediated effector cell activities, such as phagocytosis of an LY6G6F, VSIG10, TMEM25 and/or LSR expressing cells, antibody dependent cell-mediated cytotoxicity (ADCC), cytokine release, or generation of superoxide anion.

According to at least some embodiments of the invention in which the bispecific molecule is multispecific, the molecule can further include a third binding specificity, in addition to an anti-Fc binding specificity and an anti-6f binding specificity. In one embodiment, the third binding specificity is an

anti-enhancement factor (EF) portion, e.g., a molecule which binds to a surface protein involved in cytotoxic activity and thereby increases the immune response against the target cell.

The "anti-enhancement factor portion" can be an antibody, functional antibody fragment or a ligand that binds to a given molecule, e.g., an antigen or a receptor, and thereby results in an enhancement of the effect of the binding determinants for the Fc receptor or target cell antigen. The "anti-enhancement factor portion" can bind an Fc receptor or a target cell antigen. Alternatively, the anti-enhancement factor portion can bind to an entity that is different from the entity to which the first and second binding specificities bind. For example, the anti-enhancement factor portion can bind a cytotoxic T-cell (e.g., via CD2, CD3, CD8, CD28, CD4, CD40, ICAM-1 or other immune cell that results in an increased immune response against the target cell).

According to at least some embodiments of the invention, the bispecific molecules comprise as a binding specificity at least one antibody, or an antibody fragment thereof, including, e.g., an Fab, Fab', F(ab')₂, Fv, or a single chain Fv. The antibody may also be a light chain or heavy chain dimer, or any minimal fragment thereof such as a Fv or a single chain construct as described in Ladner et al. U.S. Pat. No. 4,946,778, the contents of which is expressly incorporated by reference.

In one embodiment, the binding specificity for an Fcγ receptor is provided by a monoclonal antibody, the binding of which is not blocked by human immunoglobulin G (IgG). As used herein, the term "IgG receptor" refers to any of the eight γ-chain genes located on chromosome 1. These genes encode a total of twelve transmembrane or soluble receptor isoforms which are grouped into three Fcγ receptor classes: FcγRI (CD64), FcγRII (CD32), and FcγRIII (CD16). In one preferred embodiment, the Fcγ receptor is a human high affinity FcγRI. The human FcγRI is a 72 kDa molecule, which shows high affinity for monomeric IgG (10⁸-10⁹M⁻¹).

The production and characterization of certain preferred anti-Fcγ monoclonal antibodies are described by Fanger et al. in PCT Publication WO 88/00052 and in U.S. Pat. No. 4,954,617, the teachings of which are fully incorporated by reference herein. These antibodies bind to an epitope of FcγRI, FcγRII or FcγRIII at a site which is distinct from the Fcγ binding site of the receptor and, thus, their binding is not blocked substantially by physiological levels of IgG. Specific anti-FcγRI antibodies useful in this invention are mAb 22, mAb 32, mAb 44, mAb 62 and mAb 197. The hybridoma producing mAb 32 is available from the American Type Culture Collection, ATCC Accession No. HB9469. In other embodiments, the anti-Fcγ receptor antibody is a humanized form of monoclonal antibody 22 (H22). The production and characterization of the H22 antibody is described in Graziano, R. F. et al. (1995) J. Immunol. 155 (10): 4996-5002 and PCT Publication WO 94/10332. The H22 antibody producing cell line is deposited at the American Type Culture Collection under the designation HAO22CLI and has the accession no. CRL 11177.

In still other preferred embodiments, the binding specificity for an Fc receptor is provided by an antibody that binds to a human IgA receptor, e.g., an FcαRI (FcαRI (CD89)), the binding of which is preferably not blocked by human immunoglobulin A (IgA). The term "IgA receptor" is intended to include the gene product of one α-chain gene (FcαRI) located on chromosome 19. This gene is known to encode several alternatively spliced transmembrane isoforms of 55 to 10 kDa.

FcαRI (CD89) is constitutively expressed on monocytes/macrophages, eosinophilic and neutrophilic granulocytes, but not on non-effector cell populations. FcαRI has medium affinity (Approximately 5×10⁻⁷ M⁻¹) for both IgA1 and IgA2, which is increased upon exposure to cytokines such as G-CSF or GM-CSF (Morton, H. C. et al. (1996) Critical Reviews in Immunology 16:423-440). Four FcαRI-specific monoclonal antibodies, identified as A3, A59, A62 and A77, which bind FcαRI outside the IgA ligand binding domain, have been described (Monteiro, R. C. et al. (1992) J. Immunol. 148:1764).

FcαRI and FcγRI are preferred trigger receptors for use in the bispecific molecules according to at least some embodiments of the invention because they are (1) expressed primarily on immune effector cells, e.g., monocytes, PMNs, macrophages and dendritic cells; (2) expressed at high levels (e.g., 5,000-100,000 per cell); (3) mediators of cytotoxic activities (e.g., ADCC, phagocytosis); (4) mediate enhanced antigen presentation of antigens, including self-antigens, targeted to them.

While human monoclonal antibodies are preferred, other antibodies which can be employed in the bispecific molecules according to at least some embodiments of the invention are murine, chimeric and humanized monoclonal antibodies.

The bispecific molecules of the present invention can be prepared by conjugating the constituent binding specificities, e.g., the anti-FcR and anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR binding specificities, using methods known in the art. For example, each binding specificity of the bispecific molecule can be generated separately and then conjugated to one another. When the binding specificities are proteins or peptides, a variety of coupling or cross-linking agents can be used for covalent conjugation. Examples of cross-linking agents include protein A, carbodiimide, N-succinimidyl-5-acetylthioacetate (SATA), 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB), o-phenylenedimaleimide (oPDM), N-succinimidyl-3-(2-pyridyldithio)propionate (SPDP), and sulfo-succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (sulfo-SMCC) (see e.g., Karpovsky et al. (1984) J. Exp. Med. 160:1686; Liu, M A et al. (1985) Proc. Natl. Acad. Sci. USA 82:8648). Other methods include those described in Paulus (1985) Behring Ins. Mitt. No. 78, 118-132; Brennan et al. (1985) Science 229:81-83, and Glennie et al. (1987) J. Immunol. 139: 2367-2375). Preferred conjugating agents are SATA and sulfo-SMCC, both available from Pierce Chemical Co. (Rockford, Ill.).

When the binding specificities are antibodies, they can be conjugated via sulfhydryl bonding of the C-terminus hinge regions of the two heavy chains. In a particularly preferred embodiment, the hinge region is modified to contain an odd number of sulfhydryl residues, preferably one, prior to conjugation.

Alternatively, both binding specificities can be encoded in the same vector and expressed and assembled in the same host cell. This method is particularly useful where the bispecific molecule is a mAbXmAb, mAbXFab, FabXF(ab')₂ or ligandXFab fusion protein. A bispecific molecule according to at least some embodiments of the invention can be a single chain molecule comprising one single chain antibody and a binding determinant, or a single chain bispecific molecule comprising two binding determinants. Bispecific molecules may comprise at least two single chain molecules. Methods for preparing bispecific molecules are described for example in U.S. Pat. No. 5,260,203; U.S. Pat. No. 5,455,030; U.S. Pat. No. 4,881,175; U.S. Pat. No. 5,132,405; U.S. Pat. No. 5,091,513; U.S. Pat. No. 5,476,786; U.S. Pat. No. 5,013,653; U.S. Pat. No. 5,258,498; and U.S. Pat. No. 5,482,858.

Binding of the bispecific molecules to their specific targets can be confirmed by, for example, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), FACS analysis, bioassay (e.g., growth inhibition), or Western Blot assay. Each of these assays generally detects the presence of protein-antibody complexes of particular interest by employing a labeled reagent (e.g., an antibody) specific for the complex of interest. For example, the FcR-antibody complexes can be detected using e.g., an enzyme-linked antibody or antibody fragment which recognizes and specifically binds to the antibody-FcR complexes. Alternatively, the complexes can be detected using any of a variety of other immunoassays. For example, the antibody can be radioactively labeled and used in a radioimmunoassay (RIA) (see, for example, Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986, which is incorporated by reference herein). The radioactive isotope can be detected by such means as the use of a gamma counter or a scintillation counter or by autoradiography.

Protein Modifications

Fusion Proteins

According to at least some embodiments, LY6G6F, VSIG10, TMEM25 and/or LSR fusion polypeptides have a first fusion partner comprising all or a part of a LY6G6F, VSIG10, TMEM25 and/or LSR protein fused to a second polypeptide directly or via a linker peptide sequence or a chemical linker useful to connect the two proteins. The LY6G6F, VSIG10, TMEM25 and/or LSR polypeptide may optionally be fused to a second polypeptide to form a fusion protein as described herein. The presence of the second polypeptide can alter the solubility, stability, affinity and/or valency of the LY6G6F, VSIG10, TMEM25 and/or LSR fusion polypeptide. As used herein, "valency" refers to the number of binding sites available per molecule. In one embodiment the second polypeptide is a polypeptide from a different source or different protein.

According to at least some embodiments, the LY6G6F, VSIG10, TMEM25 and/or LSR protein or fragment is selected for its activity for the treatment of immune related disorder and/or infectious disorder, and/or cancer as described herein.

In one embodiment, the second polypeptide contains one or more domains of an immunoglobulin heavy chain constant region, preferably having an amino acid sequence corresponding to the hinge, CH2 and CH3 regions of a human immunoglobulin C γ 1, C γ 2, C γ 3 or C γ 4 chain or to the hinge, CH2 and CH3 regions of a murine immunoglobulin C γ 2a chain. SEQ ID NO: 70 provides exemplary sequence for the hinge, CH2 and CH3 regions of a human immunoglobulin C γ 1.

According to at least some embodiments, the fusion protein is a dimeric fusion protein. In an optional dimeric fusion protein, the dimer results from the covalent bonding of Cys residue in the hinge region of two of the Ig heavy chains that are the same Cys residues that are disulfide linked in dimerized normal Ig heavy chains. Such proteins are referred to as LY6G6F, VSIG10, TMEM25 and/or LSR polypeptides, fragments or fusion proteins thereof.

In one embodiment, the immunoglobulin constant domain may contain one or more amino acid insertions, deletions or substitutions that enhance binding to specific cell types, increase the bioavailability, or increase the stability of the LY6G6F, VSIG10, TMEM25 and/or LSR polypeptides, fusion proteins, or fragments thereof. Suitable amino acid substitutions include conservative and non-conservative substitutions, as described above.

The fusion proteins optionally contain a domain that functions to dimerize or multimerize two or more fusion proteins. The peptide/polypeptide linker domain can either be a separate domain, or alternatively can be contained within one of the other domains (LY6G6F, VSIG10, TMEM25 and/or LSR polypeptide or second polypeptide) of the fusion protein. Similarly, the domain that functions to dimerize or multimerize the fusion proteins can either be a separate domain, or alternatively can be contained within one of the other domains (LY6G6F, VSIG10, TMEM25 and/or LSR polypeptide, second polypeptide or peptide/polypeptide linker domain) of the fusion protein. In one embodiment, the dimerization/multimerization domain and the peptide/polypeptide linker domain are the same. Further specific, illustrative and non-limiting examples of dimerization/multimerization domains and linkers are given below.

Fusion proteins disclosed herein according to at least some embodiments of the present invention are of formula I: N-R1-R2-R3-C wherein "N" represents the N-terminus of the fusion protein, "C" represents the C-terminus of the fusion protein. In the further embodiment, "R1" is a LY6G6F, VSIG10, TMEM25 and/or LSR polypeptide, "R2" is an optional peptide/polypeptide or chemical linker domain, and "R3" is a second polypeptide. Alternatively, R3 may be a LY6G6F, VSIG10, TMEM25 and/or LSR polypeptide and R1 may be a second polypeptide. Various non-limiting examples of linkers are described in greater detail below.

Optionally, the fusion protein comprises the LY6G6F, VSIG10, TMEM25 and/or LSR polypeptide fragments as described herein, fused, optionally by a linker peptide of one or more amino acids (e.g. GS) to one or more "half-life extending moieties". A "half-life extending moiety" is any moiety, for example, a polypeptide, small molecule or polymer, that, when appended to protein, extends the in vivo half-life of that protein in the body of a subject (e.g., in the plasma of the subject). For example, a half-life extending moiety is, in an embodiment of the invention, polyethylene glycol (PEG), monomethoxy PEG (mPEG) or an immunoglobulin (Ig). In an embodiment of the invention, PEG is a 5, 10, 12, 20, 30, 40 or 50 kDa moiety or larger or comprises about 12000 ethylene glycol units (PEG12000).

The fusion protein may also optionally be prepared by chemical synthetic methods and the "join" effected chemically, either during synthesis or post-synthesis. Cross-linking and other such methods may optionally be used (optionally also with the above described genetic level fusion methods), as described for example in U.S. Pat. No. 5,547,853 to Wallner et al, which is hereby incorporated by reference as if fully set forth herein as a non-limiting example only.

According to the present invention, a fusion protein may be prepared from a protein of the invention by fusion with a portion of an immunoglobulin comprising a constant region of an immunoglobulin. More preferably, the portion of the immunoglobulin comprises a heavy chain constant region which is optionally and more preferably a human heavy chain constant region. The heavy chain constant region is most preferably an IgG heavy chain constant region, and optionally and most preferably is an Fc chain, most preferably an IgG Fc fragment that comprises the hinge, CH2 and CH3 domains. The Fc chain may optionally be a known or "wild type" Fc chain, or alternatively may be mutated or truncated. The Fc portion of the fusion protein may optionally be varied by isotype or subclass, may be a chimeric or hybrid, and/or may be modified, for example to improve effector functions, control of half-life, tissue accessibility, augment biophysical characteristics such as stability, and improve efficiency of production (and less costly). Many modifications useful in

construction of disclosed fusion proteins and methods for making them are known in the art, see for example Mueller, et al, *Mol. Immun.*, 34(6):441-452 (1997), Swann, et al., *Cur. Opin. Immun.*, 20:493-499 (2008), and Presta, *Cur. Opin. Immun.* 20:460-470 (2008). In some embodiments the Fc region is the native IgG1, IgG2, or IgG4 Fc region. In some embodiments the Fc region is a hybrid, for example a chimeric consisting of IgG2/IgG4 Fc constant regions.

Modifications to the Fc region include, but are not limited to, IgG4 modified to prevent binding to Fc gamma receptors and complement, IgG1 modified to improve binding to one or more Fc gamma receptors, IgG1 modified to minimize effector function (amino acid changes), IgG1 with altered/no glycan (typically by changing expression host or substituting the Asn at position 297), and IgG1 with altered pH-dependent binding to FcRn. The Fc region may include the entire hinge region, or less than the entire hinge region.

In another embodiment, the Fc domain may contain one or more amino acid insertions, deletions or substitutions that reduce binding to the low affinity inhibitory Fc receptor CD32B (FcγRIIB) and retain wild-type levels of binding to or enhance binding to the low affinity activating Fc receptor CD16A (FcγRIIA).

Another embodiment includes IgG2-4 hybrids and IgG4 mutants that have reduced binding to FcR (Fc receptor) which increase their half life. Representative IgG2-4 hybrids and IgG4 mutants are described in Angal, S. et al., *Molecular Immunology*, 30(1):105-108 (1993); Mueller, J. et al., *Molecular Immunology*, 34(6): 441-452 (1997); and U.S. Pat. No. 6,982,323 to Wang et al. In some embodiments the IgG1 and/or IgG2 domain is deleted; for example, Angal et al. describe IgG1 and IgG2 having serine 241 replaced with a proline.

In a further embodiment, the Fc domain contains amino acid insertions, deletions or substitutions that enhance binding to CD16A. A large number of substitutions in the Fc domain of human IgG1 that increase binding to CD16A and reduce binding to CD32B are known in the art and are described in Stavenhagen, et al., *Cancer Res.*, 57(18):8882-90 (2007). Exemplary variants of human IgG1 Fc domains with reduced binding to CD32B and/or increased binding to CD16A contain F243L, R929P, Y300L, V305I or P296L substitutions. These amino acid substitutions may be present in a human IgG1 Fc domain in any combination.

In one embodiment, the human IgG1 Fc domain variant contains a F243L, R929P and Y300L substitution. In another embodiment, the human IgG1 Fc domain variant contains a F243L, R929P, Y300L, V305I and P296L substitution. In another embodiment, the human IgG1 Fc domain variant contains an N297A/Q substitution, as these mutations abolish FcγR binding. Non-limiting, illustrative, exemplary types of mutations are described in US Patent Application No. 20060034852, published on Feb. 16, 2006, hereby incorporated by reference as if fully set forth herein. The term "Fc chain" also optionally comprises any type of Fc fragment.

Several of the specific amino acid residues that are important for antibody constant region-mediated activity in the IgG subclass have been identified. Inclusion, substitution or exclusion of these specific amino acids therefore allows for inclusion or exclusion of specific immunoglobulin constant region-mediated activity. Furthermore, specific changes may result in aglycosylation for example and/or other desired changes to the Fc chain. At least some changes may optionally be made to block a function of Fc which is considered to be undesirable, such as an undesirable immune system effect, as described in greater detail below.

Non-limiting, illustrative examples of mutations to Fc which may be made to modulate the activity of the fusion protein include the following changes (given with regard to the Fc sequence nomenclature as given by Kabat, from Kabat E A et al: *Sequences of Proteins of Immunological Interest*. US Department of Health and Human Services, NIH, 1991): 220C→S; 233-238 ELLGGP→EAEGAP; 265D→A, preferably in combination with 434N→A; 297N→A (for example to block N-glycosylation); 318-322 EYKCK→AYACA; 330-331AP→SS; or a combination thereof (see for example M. Clark, "Chemical Immunol and Antibody Engineering", pp 1-31 for a description of these mutations and their effect). The construct for the Fc chain which features the above changes optionally and preferably comprises a combination of the hinge region with the CH2 and CH3 domains.

The above mutations may optionally be implemented to enhance desired properties or alternatively to block non-desired properties. For example, aglycosylation of antibodies was shown to maintain the desired binding functionality while blocking depletion of T-cells or triggering cytokine release, which may optionally be undesired functions (see M. Clark, "Chemical Immunol and Antibody Engineering", pp 1-31). Substitution of 331 proline for serine may block the ability to activate complement, which may optionally be considered an undesired function (see M. Clark, "Chemical Immunol and Antibody Engineering", pp 1-31). Changing 330 alanine to serine in combination with this change may also enhance the desired effect of blocking the ability to activate complement.

Residues 235 and 237 were shown to be involved in antibody-dependent cell-mediated cytotoxicity (ADCC), such that changing the block of residues from 233-238 as described may also block such activity if ADCC is considered to be an undesirable function.

Residue 220 is normally a cysteine for Fc from IgG1, which is the site at which the heavy chain forms a covalent linkage with the light chain. Optionally, this residue may be changed to another amino acid residue (e.g., serine), to avoid any type of covalent linkage (see M. Clark, "Chemical Immunol and Antibody Engineering", pp 1-31) or by deletion or truncation.

The above changes to residues 265 and 434 may optionally be implemented to reduce or block binding to the Fc receptor, which may optionally block undesired functionality of Fc related to its immune system functions (see "Binding site on Human IgG1 for Fc Receptors", Shields et al, Vol 276, pp 6591-6604, 2001).

The above changes are intended as illustrations only of optional changes and are not meant to be limiting in any way. Furthermore, the above explanation is provided for descriptive purposes only, without wishing to be bound by a single hypothesis.

In a further embodiment, the fusion protein includes the extracellular domain of LY6G6F, or a fragment thereof fused to an Ig Fc region. Recombinant IgLY6G6F polypeptides, fragments or fusion proteins thereof fusion proteins can be prepared by fusing the coding region of the extracellular domain of LY6G6F or a fragment thereof to the Fc region of human IgG1 or mouse IgG2a, as described previously (Chapoval, et al., *Methods Mol. Med.*, 45:247-255 (2000)).

Optionally, LY6G6F ECD refers also to fusion protein, comprising an amino acid sequence of human LY6G6F ECD fused to human immunoglobulin Fc. Optionally, said fusion protein comprises the amino acid sequence of the human LY6G6F ECD set forth in SEQ ID NO: 2 fused to human IgG1 Fc set forth in any one of SEQ ID NOs:70, 156. Option-

ally, the amino acid sequence of said fusion protein is set forth in SEQ ID NO:71 or SEQ ID NO:172.

In a further embodiment, the fusion protein includes the extracellular domain of VSIG10, or a fragment thereof fused to an Ig Fc region. Recombinant IgVSIG10 polypeptides, fragments or fusion proteins thereof fusion proteins can be prepared by fusing the coding region of the extracellular domain of VSIG10 or a fragment thereof to the Fc region of human IgG1 or mouse IgG2a, as described previously (Chapoval, et al., Methods Mol. Med, 45:247-255 (2000)).

Optionally, VSIG10 ECD refers also to fusion protein, comprising an amino acid sequence of human VSIG10 ECD fused to human immunoglobulin Fc. Optionally, said fusion protein comprises the amino acid sequence of the human VSIG10 ECD, selected from the amino acid sequences set forth in any one of SEQ ID NOs: 4 and 6, fused to human IgG1 Fc set forth in any one of SEQ ID NOs:70, 156. Optionally, the amino acid sequence of said fusion protein is set forth in any one of SEQ ID NOs:72, 73, 173 and 174.

In a further embodiment, the fusion protein includes the extracellular domain of TMEM25, or a fragment thereof fused to an Ig Fc region. Recombinant IgTMEM25 polypeptides, fragments or fusion proteins thereof fusion proteins can be prepared by fusing the coding region of the extracellular domain of TMEM25 or a fragment thereof to the Fc region of human IgG1 or mouse IgG2a, as described previously (Chapoval, et al., Methods Mol. Med, 45:247-255 (2000)).

Optionally, TMEM25 ECD refers also to fusion protein, comprising an amino acid sequence of human TMEM25 ECD fused to human immunoglobulin Fc. Optionally, said fusion protein comprises the amino acid sequence of the human TMEM25 ECD set forth in SEQ ID NO: 8 fused to human IgG1 Fc set forth in any one of SEQ ID NOs:70, 156. Optionally, the amino acid sequence of said fusion protein is set forth in any one of SEQ ID NOs:74, 175.

In a further embodiment, the fusion protein includes the extracellular domain of LSR, or a fragment thereof fused to an Ig Fc region. Recombinant Ig LSR polypeptides, fragments or fusion proteins thereof fusion proteins can be prepared by fusing the coding region of the extracellular domain of LSR or a fragment thereof to the Fc region of human IgG1 or mouse IgG2a, as described previously (Chapoval, et al., Methods Mol. Med, 45:247-255. (2000)).

Optionally, LSR ECD refers also to fusion protein, comprising an amino acid sequence of human LSR ECD fused to human immunoglobulin Fc. Optionally, said fusion protein comprises the amino acid sequence of the human LSR ECD,

The disclosed fusion proteins can be isolated using standard molecular biology techniques. For example, an expression vector containing a DNA sequence encoding a LY6G6F, VSIG10, TMEM25 and/or LSR polypeptides, fragments or fusion proteins thereof fusion protein is transfected into 293 cells by calcium phosphate precipitation and cultured in serum-free DMEM. The supernatant is collected at 72 h and the fusion protein is purified by Protein G, or preferably Protein A SEPHAROSE® columns (Pharmacia, Uppsala, Sweden). Optionally, a DNA sequence encoding a LY6G6F, VSIG10, TMEM25 and/or LSR polypeptides, fragments or fusion proteins thereof fusion protein is transfected into GPEx® retrovectors and expressed in CHO-S cells following four rounds of retrovector transduction. The protein is clarified from supernatants using protein A chromatography.

In another embodiment the second polypeptide may have a conjugation domain through which additional molecules can be bound to the LY6G6F, VSIG10, TMEM25 and/or LSR fusion proteins. In one such embodiment, the conjugated molecule is capable of targeting the fusion protein to a particular organ or tissue; further specific, illustrative, non-limiting examples of such targeting domains and/or molecules are given below.

In another such embodiment the conjugated molecule is another immunomodulatory agent that can enhance or augment the effects of the LY6G6F, VSIG10, TMEM25 and/or LSR fusion protein. In another embodiment the conjugated molecule is Polyethylene Glycol (PEG).

Peptide or Polypeptide Linker Domain

The disclosed LY6G6F, VSIG10, TMEM25 and/or LSR fusion proteins optionally contain a peptide or polypeptide linker domain that separates the LY6G6F, VSIG10, TMEM25 and/or LSR polypeptide from the second polypeptide. In one embodiment, the linker domain contains the hinge region of an immunoglobulin. In a further embodiment, the hinge region is derived from a human immunoglobulin. Suitable human immunoglobulins that the hinge can be derived from include IgG, IgD and IgA. In a further embodiment, the hinge region is derived from human IgG. Amino acid sequences of immunoglobulin hinge regions and other domains are well known in the art. In one embodiment, LY6G6F, VSIG10, TMEM25 and/or LSR fusion polypeptides contain the hinge, CH2 and CH3 regions of a human immunoglobulin Cγ1 chain, optionally with the Cys at position 220 (according to full length human IgG1, position 5 in SEQ ID NO:70) replaced with a Ser (SEQ ID NO: 156) having at least 85%, 90%, 95%, 99% or 100% sequence homology to amino acid sequence set forth in SEQ ID NO:70:

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EPKSCDKTHTCPPCPAPELGGPSVFLPCKPKDTLMI SRTPEVTCVVVDVSHEDPEVKENNYVDGVEVHNA
KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSQSVMEHA
LHNHYTQKSLSLSPGK
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selected from the amino acid sequences set forth in any one of SEQ ID NOs: 12, 14, 15, 16, 17, 18, 47, 48, 49 and 50, fused to human IgG1 Fc set forth in any one of SEQ ID NOs:70, 156. Optionally, the amino acid sequence of said fusion protein is set forth in any one of SEQ ID NOs:75, 76, 77, 78, 79, 80, 176, 177, 178, 179, 180, and 181.

The aforementioned exemplary fusion proteins can incorporate any combination of the variants described herein. In another embodiment the terminal lysine of the aforementioned exemplary fusion proteins is deleted.

The hinge can be further shortened to remove amino acids 1, 2, 3, 4, 5, or combinations thereof of any one of SEQ ID NOs: 70 or 156. In one embodiment, amino acids 1-5 of any one of SEQ ID NOs: 70 or 156 are deleted. Exemplary LY6G6F, VSIG10, TMEM25 and/or LSR fusion polypeptides comprised of the hinge, CH2 and CH3 regions of a human immunoglobulin Cγ1 chain with the Cys at position 220 replaced with a Ser are set forth in SEQ ID NOs:71, 72, 73, 74, 75, 76, 77, 78, 79, 80.

In another embodiment, LY6G6F, VSIG10, TMEM25 and/or LSR fusion polypeptides contain the CH2 and CH3 regions

of a human immunoglobulin C γ 1 chain having at least 85%, 90%, 95%, 99% or 100% sequence homology to amino acid sequence set forth in SEQ ID NO: 157: APELLGGPSVFLF-PPKPKDITLMISRTPEVTCVVVDVSHED-PEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVS-VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLT-CLVKGFPYSDIAVEWESNGQPENNYKTT PPVLDS-DGSFFLYSKLTVDKSRWQQGNVFCFSVM-HEALHNHYTQKSLSLSPGK In another embodiment, the LY6G6F, VSIG10, TMEM25 and/or LSR fusion polypeptides contain the CH2 and CH3 regions of a murine immunoglobulin C γ 2a chain at least 85%, 90%, 95%, 99% or 100% sequence homology to amino acid sequence set forth in SEQ ID NO: 158: EPRGPTIKPCPPCKCPAPNLLGGPS-VFIFPPKIKDVLMSLSPIVTCVVVDVSEDDPD VQISWFVNNVEVHTAQTQTHREDYNSTL-RVVSALPIQHQQDWMMSGKEFKCKVNN KDLPIER-TISKPKGSVRAPQVYVLPPEEEMT-KKQVTLTCMVTDFMPEDIYVE WTNNGKTELNYKNTEPVLDSDGSY-FMYSKLRVEKKNWVERNSYSYSCSVVHEGLH NHHT-TKSFRTPGK. In another embodiment, the linker domain contains a hinge region of an immunoglobulin as described above, and further includes one or more additional immunoglobulin domains.

Other suitable peptide/polypeptide linker domains include naturally occurring or non-naturally occurring peptides or polypeptides. Peptide linker sequences are at least 2 amino acids in length. Optionally the peptide or polypeptide domains are flexible peptides or polypeptides. A "flexible linker" herein refers to a peptide or polypeptide containing two or more amino acid residues joined by peptide bond(s) that provides increased rotational freedom for two polypeptides linked thereby than the two linked polypeptides would have in the absence of the flexible linker. Such rotational freedom allows two or more antigen binding sites joined by the flexible linker to each access target antigen(s) more efficiently. Exemplary flexible peptides/polypeptides include, but are not limited to, the amino acid sequences Gly-Ser (SEQ ID NO: 159), Gly-Ser-Gly-Ser (SEQ ID NO: 160), Ala-Ser (SEQ ID NO: 161), Gly-Gly-Gly-Ser (SEQ ID NO: 162), Gly4-Ser (SEQ ID NO: 163), (Gly4-Ser)₂ (SEQ ID NO: 164), (Gly4-Ser)₃ (SEQ ID NO: 165) and (Gly4-Ser)₄ (SEQ ID NO: 166). Additional flexible peptide/polypeptide sequences are well known in the art. Other suitable peptide linker domains include helix forming linkers such as Ala-(Glu-Ala-Ala-Ala-Lys)_n-Ala (n=1-5). Additional helix forming peptide/polypeptide sequences are well known in the art. Non-limiting examples of such linkers are depicted in SEQ ID NO: 167-171.

Dimerization, Multimerization and Targeting Domains

The fusion proteins disclosed herein optionally contain a dimerization or multimerization domain that functions to dimerize or multimerize two or more fusion proteins. The domain that functions to dimerize or multimerize the fusion proteins can either be a separate domain, or alternatively can be contained within one of the other domains (LY6G6F, VSIG10, TMEM25 and/or LSR polypeptide, second polypeptide, or peptide/polypeptide linker domain) of the fusion protein.

Dimerization or multinierization can occur between or among two or more fusion proteins through dimerization or multimerization domains. Alternatively, dimerization or multimerization of fusion proteins can occur by chemical crosslinking. The dimers or multimers that are formed can be homodimeric/homomultimeric or heterodimeric/heteromul-

timeric. The second polypeptide "partner" in the LY6G6F, VSIG10, TMEM25 and/or LSR fusion polypeptides may be comprised of one or more other proteins, protein fragments or peptides as described herein, including but not limited to any immunoglobulin (Ig) protein or portion thereof, preferably the Fc region, or a portion of a biologically or chemically active protein such as the papillomavirus E7 gene product, melanoma-associated antigen p97, and HIV env protein (gp120). The "partner" is optionally selected to provide a soluble dimer/multimer and/or for one or more other biological activities as described herein.

A "dimerization domain" is formed by the association of at least two amino acid residues or of at least two peptides or polypeptides (which may have the same, or different, amino acid sequences). The peptides or polypeptides may interact with each other through covalent and/or non-covalent associations). Optional dimerization domains contain at least one cysteine that is capable of forming an intermolecular disulfide bond with a cysteine on the partner fusion protein. The dimerization domain can contain one or more cysteine residues such that disulfide bond(s) can form between the partner fusion proteins. In one embodiment, dimerization domains contain one, two or three to about ten cysteine residues. In a further embodiment, the dimerization domain is the hinge region of an immunoglobulin.

Additional exemplary dimerization domains can be any known in the art and include, but not limited to, coiled coils, acid patches, zinc fingers, calcium hands, a C_H1-C_L pair, an "interface" with an engineered "knob" and/or "protruberance" as described in U.S. Pat. No. 5,821,333, leucine zippers (e.g., from jun and/or fos) (U.S. Pat. No. 5,932,448), and/or the yeast transcriptional activator GCN4, SH2 (src homology 2), SH3 (src Homology 3) (Vidal, et al, Biochemistry, 43, 7336-44 ((2004)), phosphotyrosine binding (PTB) (Zhou, et al., Nature, 378:584-592 (1995)), WW (Sudol, Prog, Biochys. Mol. Bio., 65:113-132 (1996)), PDZ (Kim, et al., Nature, 378: 85-88 (1995); Komau, et al, Science, 269:1737-1740 (1995)) 14-3-3, WD40 (Hu5 et al., J Biol. Chem., 273, 33489-33494 (1998)) EH, Lim, an isoleucine zipper, a receptor dimer pair (e.g., interleukin-8 receptor (IL-8R); and integrin heterodimers such as LFA-I and GPIIb/IIIa), or the dimerization region(s) thereof, dimeric ligand polypeptides (e.g. nerve growth factor (NGF), neurotrophin-3 (NT-3), interleukin-8 (IL-8), vascular endothelial growth factor (VEGF), VEGF-C, VEGF-D, PDGF members, and brain-derived neurotrophic factor (BDNF) (Arakawa, et al., J Biol. Chem., 269(45): 27833-27839 (1994) and Radziejewski, et al., Biochem., 32(48): 1350 (1993)) and can also be variants of these domains in which the affinity is altered. The polypeptide pairs can be identified by methods known in the art, including yeast two hybrid screens. Yeast two hybrid screens are described in U.S. Pat. Nos. 5,283,173 and 6,562,576. Affinities between a pair of interacting domains can be determined using methods known in the art, including as described in Katahira, et al, J. Biol Chem, 277, 9242-9246 (2002)). Alternatively, a library of peptide sequences can be screened for heterodimerization, for example, using the methods described in WO 01/00814. Useful methods for protein-protein interactions are also described in U.S. Pat. No. 6,790,624.

A "multimerization domain" is a domain that causes three or more peptides or polypeptides to interact with each other through covalent and/or non-covalent association(s). Suitable multimerization domains include, but are not limited to, coiled-coil domains. A coiled-coil is a peptide sequence with a contiguous pattern of mainly hydrophobic residues spaced 3 and 4 residues apart, usually in a sequence of seven amino acids (heptad repeat) or eleven amino acids (undecad repeat),

which assembles (folds) to form a multimeric bundle of helices. Coiled-coils with sequences including some irregular distribution of the 3 and 4 residues spacing are also contemplated. Hydrophobic residues are in particular the hydrophobic amino acids Val, Ile, Leu, Met, Tyr, Phe and Trp. "Mainly hydrophobic" means that at least 50% of the residues must be selected from the mentioned hydrophobic amino acids.

The coiled coil domain may be derived from laminin. In the extracellular space, the heterotrimeric coiled coil protein laminin plays an important role in the formation of basement membranes. Apparently, the multifunctional oligomeric structure is required for laminin function. Coiled coil domains may also be derived from the thrombospondins in which three (TSP-1 and TSP-2) or five (TSP-3, TSP-4 and TSP-5) chains are connected, or from COMP (COMPcc) (Guo, et al., EMBO J, 1998, 17: 5265-5272) which folds into a parallel five-stranded coiled coil (Malashkevich, et al., Science, 274: 761-765 (1996)). Additional non limiting examples of coiled-coil domains derived from other proteins, and other domains that mediate polypeptide multimerization are known in the art such as the vasodilator-stimulated phosphoprotein (VASP) domain, matrilin-1 (CMP), viral fusion peptides, soluble NSF (N-ethylmaleimide-sensitive factor) Attachment Protein receptor (SNARE) complexes, leucine-rich repeats, certain tRNA synthetases, are suitable for use in the disclosed fusion proteins.

In another embodiment, LY6G6F, VSIG10, TMEM25 and/or LSR polypeptides, fusion proteins, or fragments thereof can be induced to form multimers by binding to a second multivalent polypeptide, such as an antibody. Antibodies suitable for use to multimerize LY6G6F, VSIG10, TMEM25 and/or LSR polypeptides, fusion proteins, or fragments thereof include, but are not limited to, IgM antibodies and cross-linked, multivalent IgG, IgA, IgD, or IgE complexes.

Dimerization or multimerization can occur between or among two or more fusion proteins through dimerization or multimerization domains, including those described above. Alternatively, dimerization or multimerization of fusion proteins can occur by chemical crosslinking. Fusion protein dimers can be homodimers or heterodimers. Fusion protein multimers can be homomultimers or heteromultimers. Fusion protein dimers as disclosed herein are of formula II: N-R1-R2-R3-C or, alternatively, are of formula III: N-R1-R2-R3-C

C-R4-R5-R6-N wherein the fusion proteins of the dimer provided by formula II are defined as being in a parallel orientation and the fusion proteins of the dimer provided by formula III are defined as being in an antiparallel orientation. Parallel and antiparallel dimers are also referred to as cis and trans dimers, respectively. "N" and "C" represent the N- and C-termini of the fusion protein, respectively. The fusion protein constituents "R1", "R2" and "R3" are as defined above with respect to formula I. With respect to both formula II and formula III, "R4" is a LY6G6F, VSIG10, TMEM25 and/or LSR polypeptide or a second polypeptide, "R5" is an optional peptide/polypeptide linker domain, and "R6" is a LY6G6F, VSIG10, TMEM25 and/or LSR polypeptide or a second polypeptide, wherein "R6" is a LY6G6F, VSIG10, TMEM25 and/or LSR polypeptide when "R4" is a second polypeptide, and "R6" is a second polypeptide when "R4" is a LY6G6F, VSIG10, TMEM25 and/or LSR polypeptide. In one embodiment, "R1" is a LY6G6F, VSIG10, TMEM25 and/or LSR polypeptide, "R4" is also a LY6G6F, VSIG10, TMEM25 and/or LSR polypeptide, and "R3" and "R6" are both second polypeptides.

Fusion protein dimers of formula II are defined as homodimers when "R1"="R4", "R2"="R5" and "R3"="R6". Similarly, fusion protein dimers of formula III are defined as homodimers when "R1"="R6", "R2"="R5" and "R3"="R4".

5 Fusion protein dimers are defined as heterodimers when these conditions are not met for any reason. For example, heterodimers may contain domain orientations that meet these conditions (i.e., for a dimer according to formula II, "R1" and "R4" are both LY6G6F, VSIG10, TMEM25 and/or LSR polypeptides, "R2" and "R5" are both peptide/polypeptide linker domains and "R3" and "R6" are both second polypeptides), however the species of one or more of these domains is not identical. For example, although "R3" and "R6" may both be LY6G6F, VSIG10, TMEM25 and/or LSR polypeptides, one polypeptide may contain a wild-type LY6G6F, VSIG10, TMEM25 and/or LSR amino acid sequence while the other polypeptide may be a variant LY6G6F, VSIG10, TMEM25 and/or LSR polypeptide. An exemplary variant LY6G6F, VSIG10, TMEM25 and/or LSR polypeptide is LY6G6F, VSIG10, TMEM25 and/or LSR polypeptide that has been modified to have increased or decreased binding to a target cell, increased activity on immune cells, increased or decreased half life or stability. Dimers of fusion proteins that contain either a CHI or CL region of an immunoglobulin as part of the polypeptide linker domain preferably form heterodimers wherein one fusion protein of the dimer contains a CHI region and the other fusion protein of the dimer contains a CL region.

Fusion proteins can also be used to form multimers. As with dimers, multimers may be parallel multimers, in which all fusion proteins of the multimer are aligned in the same orientation with respect to their N- and C-termini. Multimers may be antiparallel multimers, in which the fusion proteins of the multimer are alternatively aligned in opposite orientations with respect to their N- and C-termini. Multimers (parallel or antiparallel) can be either homomultimers or heteromultimers. The fusion protein is optionally produced in dimeric form; more preferably, the fusion is performed at the genetic level as described below, by joining polynucleotide sequences corresponding to the two (or more) proteins, portions of proteins and/or peptides, such that a joined or fused protein is produced by a cell according to the joined polynucleotide sequence. A description of preparation for such fusion proteins is described with regard to U.S. Pat. No. 5,851,795 to Linsley et al, which is hereby incorporated by reference as if fully set forth herein as a non-limiting example only.

Targeting Domains

The LY6G6F, VSIG10, TMEM25 and/or LSR polypeptides and fusion proteins can contain a targeting domain to target the molecule to specific sites in the body. Optional targeting domains target the molecule to areas of inflammation. Exemplary targeting domains are antibodies, or antigen binding fragments thereof that are specific for inflamed tissue or to a proinflammatory cytokine including but not limited to IL17, IL-4, IL-6, IL-12, IL-21, IL-22, and IL-23. In the case of neurological disorders such as Multiple Sclerosis, the targeting domain may target the molecule to the CNS or may bind to VCAM-1 on the vascular epithelium. Additional targeting domains can be peptide aptamers specific for a proinflammatory molecule. In other embodiments, the LY6G6F, VSIG10, TMEM25 and/or LSR fusion protein can include a binding partner specific for a polypeptide displayed on the surface of an immune cell, for example a T cell. In still other embodiments, the targeting domain specifically targets activated immune cells. Optional immune cells that are targeted include Th0, Th1, Th17, Th2 and Th22 T cells, other cells that

secrete, or cause other cells to secrete inflammatory molecules including, but not limited to, IL-1 beta, TNF-alpha, TGF-beta, IFN-gamma, IL-17, IL-6, IL-23, IL-22, IL-21, and MMPs, and Tregs. For example, a targeting domain for Tregs may bind specifically to CD25. The above changes are intended as illustrations only of optional changes and are not meant to be limiting in any way. Furthermore, the above explanation is provided for descriptive purposes only, without wishing to be bound by a single hypothesis.

Addition of Groups

If a protein according to the present invention is a linear molecule, it is possible to place various functional groups at various points on the linear molecule which are susceptible to or suitable for chemical modification. Functional groups can be added to the termini of linear forms of the protein according to at least some embodiments of the invention. In some embodiments, the functional groups improve the activity of the protein with regard to one or more characteristics, including but not limited to, improvement in stability, penetration (through cellular membranes and/or tissue barriers), tissue localization, efficacy, decreased clearance, decreased toxicity, improved selectivity, improved resistance to expulsion by cellular pumps, and the like. For convenience sake and without wishing to be limiting, the free N-terminus of one of the sequences contained in the compositions according to at least some embodiments of the invention will be termed as the N-terminus of the composition, and the free C-terminal of the sequence will be considered as the C-terminus of the composition. Either the C-terminus or the N-terminus of the sequences, or both, can be linked to a carboxylic acid functional groups or an amine functional group, respectively.

Non-limiting examples of suitable functional groups are described in Green and Wuts, "Protecting Groups in Organic Synthesis", John Wiley and Sons, Chapters 5 and 7, 1991, the teachings of which are incorporated herein by reference. Preferred protecting groups are those that facilitate transport of the active ingredient attached thereto into a cell, for example, by reducing the hydrophilicity and increasing the lipophilicity of the active ingredient, these being an example for "a moiety for transport across cellular membranes".

These moieties can optionally and preferably be cleaved in vivo, either by hydrolysis or enzymatically, inside the cell. (Ditter et al., J. Pharm. Sci. 57:783 (1968); Ditter et al., J. Pharm. Sci. 57:828 (1968); Ditter et al., J. Pharm. Sci. 58:557 (1969); King et al., Biochemistry 26:2294 (1987); Lindberg et al., Drug Metabolism and Disposition 17:311 (1989); and Tunek et al., Biochem. Pharm. 37:3867 (1988), Anderson et al., Arch. Biochem. Biophys. 239:538 (1985) and Singhal et al., FASEB J. 1:220 (1987)). Hydroxyl protecting groups include esters, carbonates and carbamate protecting groups. Amine protecting groups include alkoxy and aryloxy carbonyl groups, as described above for N-terminal protecting groups. Carboxylic acid protecting groups include aliphatic, benzylic and aryl esters, as described above for C-terminal protecting groups. In one embodiment, the carboxylic acid group in the side chain of one or more glutamic acid or aspartic acid residue in a composition of the present invention is protected, preferably with a methyl, ethyl, benzyl or substituted benzyl ester, more preferably as a benzyl ester.

Non-limiting, illustrative examples of N-terminal protecting groups include acyl groups ($-\text{CO}-\text{R}_1$) and alkoxy carbonyl or aryloxy carbonyl groups ($-\text{CO}-\text{O}-\text{R}_1$), wherein R_1 is an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aromatic or a substituted aromatic group. Specific examples of acyl groups include but are not limited to acetyl, (ethyl)-CO-, n-propyl-CO-, iso-propyl-CO-, n-butyl-CO-, sec-butyl-CO-, t-butyl-CO-, hexyl, lauroyl, palmi-

toyl, myristoyl, stearyl, oleoyl phenyl-CO-, substituted phenyl-CO-, benzyl-CO- and (substituted benzyl)-CO-. Examples of alkoxy carbonyl and aryloxy carbonyl groups include $\text{CH}_3-\text{O}-\text{CO}-$, (ethyl)-O-CO-, n-propyl-O-CO-, iso-propyl-O-CO-, n-butyl-O-CO-, sec-butyl-O-CO-, t-butyl-O-CO-, phenyl-O-CO-, substituted phenyl-O-CO- and benzyl-O-CO-, (substituted benzyl)-O-CO-, Adamantan, naphthalen, myristoleyl, toluen, biphenyl, cinnamoyl, nitrobenzoy, toluoyl, furoyl, benzoyl, cyclohexane, norbornane, or Z-caproic. In order to facilitate the N-acylation, one to four glycine residues can be present in the N-terminus of the molecule.

The carboxyl group at the C-terminus of the compound can be protected, for example, by a group including but not limited to an amide (i.e., the hydroxyl group at the C-terminus is replaced with $-\text{NH}_2$, $-\text{NHR}_2$ and $-\text{NR}_2\text{R}_3$) or ester (i.e. the hydroxyl group at the C-terminus is replaced with $-\text{OR}_2$). R_2 and R_3 are optionally independently an aliphatic, substituted aliphatic, benzyl, substituted benzyl, aryl or a substituted aryl group. In addition, taken together with the nitrogen atom, R_2 and R_3 can optionally form a C4 to C8 heterocyclic ring with from about 0-2 additional heteroatoms such as nitrogen, oxygen or sulfur. Non-limiting suitable examples of suitable heterocyclic rings include piperidinyl, pyrrolidinyl, morpholino, thiomorpholino or piperazinyl. Examples of C-terminal protecting groups include but are not limited to $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{NH}(\text{ethyl})$, $-\text{N}(\text{ethyl})_2$, $-\text{N}(\text{methyl})(\text{ethyl})$, $-\text{NH}(\text{benzyl})$, $-\text{N}(\text{C1-C4 alkyl})(\text{benzyl})$, $-\text{NH}(\text{phenyl})$, $-\text{N}(\text{C1-C4 alkyl})(\text{phenyl})$, $-\text{OCH}_3$, $-\text{O}(\text{ethyl})$, $-\text{O}(\text{n-propyl})$, $-\text{O}(\text{n-butyl})$, $-\text{O}(\text{iso-propyl})$, $-\text{O}(\text{sec-butyl})$, $-\text{O}(\text{t-butyl})$, $-\text{O-benzyl}$ and $-\text{O-phenyl}$.

Substitution by Peptidomimetic Moieties

A "peptidomimetic organic moiety" can optionally be substituted for amino acid residues in the composition of this invention both as conservative and as non-conservative substitutions. These moieties are also termed "non-natural amino acids" and may optionally replace amino acid residues, amino acids or act as spacer groups within the peptides in lieu of deleted amino acids. The peptidomimetic organic moieties optionally and preferably have steric, electronic or configurational properties similar to the replaced amino acid and such peptidomimetics are used to replace amino acids in the essential positions, and are considered conservative substitutions. However such similarities are not necessarily required. According to preferred embodiments of the present invention, one or more peptidomimetics are selected such that the composition at least substantially retains its physiological activity as compared to the native protein according to the present invention.

Peptidomimetics may optionally be used to inhibit degradation of the peptides by enzymatic or other degradative processes. The peptidomimetics can optionally and preferably be produced by organic synthetic techniques. Non-limiting examples of suitable peptidomimetics include D amino acids of the corresponding L amino acids, tetrazol (Zabrocki et al., J. Am. Chem. Soc. 110:5875-5880 (1988)); isosteres of amide bonds (Jones et al., Tetrahedron Lett. 29: 3853-3856 (1988)); LL-3-amino-2-propenidone-6-carboxylic acid (LL-Acp) (Kemp et al., J. Org. Chem. 50:5834-5838 (1985)). Similar analogs are shown in Kemp et al., Tetrahedron Lett. 29:5081-5082 (1988) as well as Kemp et al., Tetrahedron Lett. 29:5057-5060 (1988), Kemp et al., Tetrahedron Lett. 29:4935-4938 (1988) and Kemp et al., J. Org. Chem. 54:109-115 (1987). Other suitable but exemplary peptidomimetics are shown in Nagai and Sato, Tetrahedron Lett. 26:647-650 (1985); Di Maio et al., J. Chem. Soc. Perkin Trans., 1687

(1985); Kahn et al., *Tetrahedron Lett.* 30:2317 (1989); Olson et al., *J. Am. Chem. Soc.* 112:323-333 (1990); Garvey et al., *J. Org. Chem.* 56:436 (1990). Further suitable exemplary peptidomimetics include hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (Miyake et al., *J. Takeda Res. Labs* 43:53-76 (1989)); 1,2,3,4-tetrahydro-isoquinoline-3-carboxylate (Kazmierski et al., *J. Am. Chem. Soc.* 133:2275-2283 (1991)); histidine isoquinolone carboxylic acid (HIC) (Zechel et al., *Int. J. Pep. Protein Res.* 43 (1991)); (2S,3S)-methyl-phenylalanine, (2S,3R)-methyl-phenylalanine, (2R, 3S)-methyl-phenylalanine and (2R,3R)-methyl-phenylalanine (Kazmierski and Hruby, *Tetrahedron Lett.* (1991)).

Exemplary, illustrative but non-limiting non-natural amino acids include beta-amino acids (beta3 and beta2), homo-amino acids, cyclic amino acids, aromatic amino acids, Pro and Pyr derivatives, 3-substituted Alanine derivatives, Glycine derivatives, ring-substituted Phe and Tyr Derivatives, linear core amino acids or diamino acids. They are available from a variety of suppliers, such as Sigma-Aldrich (USA) for example.

Protein Chemical Modifications

In the present invention any part of a protein according to at least some embodiments of the invention may optionally be chemically modified, i.e. changed by addition of functional groups. For example the side amino acid residues appearing in the native sequence may optionally be modified, although as described below alternatively other parts of the protein may optionally be modified, in addition to or in place of the side amino acid residues. The modification may optionally be performed during synthesis of the molecule if a chemical synthetic process is followed, for example by adding a chemically modified amino acid. However, chemical modification of an amino acid when it is already present in the molecule ("in situ" modification) is also possible.

The amino acid of any of the sequence regions of the molecule can optionally be modified according to any one of the following exemplary types of modification (in the peptide conceptually viewed as "chemically modified"). Non-limiting exemplary types of modification include carboxymethylation, acylation, phosphorylation, glycosylation or fatty acylation. Ether bonds can optionally be used to join the serine or threonine hydroxyl to the hydroxyl of a sugar. Amide bonds can optionally be used to join the glutamate or aspartate carboxyl groups to an amino group on a sugar (Garg and Jeanloz, *Advances in Carbohydrate Chemistry and Biochemistry*, Vol. 43, Academic Press (1985); Kunz, *Ang. Chem. Int. Ed. English* 26:294-308 (1987)). Acetal and ketal bonds can also optionally be formed between amino acids and carbohydrates. Fatty acid acyl derivatives can optionally be made, for example, by acylation of a free amino group (e.g., lysine) (Toth et al., *Peptides: Chemistry, Structure and Biology*, Rivier and Marshal, eds., ESCOM Publ., Leiden, 1078-1079 (1990)).

As used herein the term "chemical modification", when referring to a protein or peptide according to the present invention, refers to a protein or peptide where at least one of its amino acid residues is modified either by natural processes, such as processing or other post-translational modifications, or by chemical modification techniques which are well known in the art. Examples of the numerous known modifications typically include, but are not limited to: acetylation, acylation, amidation, ADP-ribosylation, glycosylation, GPI anchor formation, covalent attachment of a lipid or lipid derivative, methylation, myristylation, pegylation, prenylation, phosphorylation, ubiquitination, or any similar process.

Other types of modifications optionally include the addition of a cycloalkane moiety to a biological molecule, such as a protein, as described in PCT Application No. WO 2006/050262, hereby incorporated by reference as if fully set forth herein. These moieties are designed for use with biomolecules and may optionally be used to impart various properties to proteins.

Furthermore, optionally any point on a protein may be modified. For example, pegylation of a glycosylation moiety on a protein may optionally be performed, as described in PCT Application No. WO 2006/050247, hereby incorporated by reference as if fully set forth herein. One or more polyethylene glycol (PEG) groups may optionally be added to O-linked and/or N-linked glycosylation. The PEG group may optionally be branched or linear. Optionally any type of water-soluble polymer may be attached to a glycosylation site on a protein through a glycosyl linker.

Altered Glycosylation

Proteins according to at least some embodiments of the invention may be modified to have an altered glycosylation pattern (i.e., altered from the original or native glycosylation pattern). As used herein, "altered" means having one or more carbohydrate moieties deleted, and/or having at least one glycosylation site added to the original protein.

Glycosylation of proteins is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences, asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-acetyl-galactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

Addition of glycosylation sites to proteins according to at least some embodiments of the invention is conveniently accomplished by altering the amino acid sequence of the protein such that it contains one or more of the above-described tripeptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues in the sequence of the original protein (for O-linked glycosylation sites). The protein's amino acid sequence may also be altered by introducing changes at the DNA level.

Another means of increasing the number of carbohydrate moieties on proteins is by chemical or enzymatic coupling of glycosides to the amino acid residues of the protein. Depending on the coupling mode used, the sugars may be attached to (a) arginine and histidine, (b) free carboxyl groups, (c) free sulfhydryl groups such as those of cysteine, (d) free hydroxyl groups such as those of serine, threonine, or hydroxyproline, (e) aromatic residues such as those of phenylalanine, tyrosine, or tryptophan, or (f) the amide group of glutamine. These methods are described in WO 87/05330, and in Aplin and Wriston, *CRC Crit. Rev. Biochem.*, 22: 259-306 (1981).

Removal of any carbohydrate moieties present on proteins according to at least some embodiments of the invention may be accomplished chemically or enzymatically. Chemical deglycosylation requires exposure of the protein to trifluoromethanesulfonic acid, or an equivalent compound. This treatment results in the cleavage of most or all sugars except the linking sugar (N-acetylglucosamine or N-acetylgalactosamine), leaving the amino acid sequence intact.

Chemical deglycosylation is described by Hakimuddin et al., *Arch. Biochem. Biophys.*, 259: 52 (1987); and Edge et al., *Anal. Biochem.*, 118: 131 (1981). Enzymatic cleavage of carbohydrate moieties on proteins can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura et al., *Meth. Enzymol.*, 138: 350 (1987).

Methods of Use

As used herein "therapeutic agent" is any one of the LY6G6F, VSIG10, TMEM25 and/or LSR proteins and polypeptides according to at least some embodiments of the present invention, or orthologs, or fragments thereof, especially the ectodomain or secreted forms of LY6G6F, VSIG10, TMEM25 and/or LSR proteins, and/or fusion protein, and/or multimeric protein containing same, or nucleic acid sequence or fragments thereof of LY6G6F, VSIG10, TMEM25 and/or LSR, as well as drugs which specifically bind to the LY6G6F, VSIG10, TMEM25 and/or LSR proteins, and/or drugs which agonize or antagonize the binding of other moieties to the LY6G6F, VSIG10, TMEM25 and/or LSR proteins, and/or drugs which modulate (agonize or antagonize) at least one LY6G6F, VSIG10, TMEM25 and/or LSR related biological activity. Such drugs include monoclonal and/or polyclonal antibodies, and/or antigen binding fragments, and/or conjugates containing same, and/or alternative scaffolds, thereof comprising an antigen binding site that binds specifically to any one of the LY6G6F, VSIG10, TMEM25 and/or LSR polypeptides or an epitope thereof. Such drugs by way of example also include small molecules, peptides, ribozymes, aptamers, antisense molecules, siRNA's and the like.

Stimulation of activity of LY6G6F, VSIG10, TMEM25 and/or LSR is desirable in situations in which LY6G6F, VSIG10, TMEM25 and/or LSR is abnormally downregulated, and/or situations in which increased activity of LY6G6F, VSIG10, TMEM25 and/or LSR is likely to have a beneficial effect. Likewise, inhibition of activity of LY6G6F, VSIG10, TMEM25 and/or LSR is desirable in situations in which LY6G6F, VSIG10, TMEM25 and/or LSR is abnormally upregulated, and/or situations in which decreased activity of LY6G6F, VSIG10, TMEM25 and/or LSR is likely to have beneficial effect.

As mentioned herein above, the therapeutic agents can be used to treat immune related disorders as recited herein, and/or autoimmune disorders as recited herein, and/or infectious disorders as recited herein, and/or cancer as recited herein and/or for blocking and/or promoting immune costimulation mediated by any one of the LY6G6F, VSIG10, TMEM25 and/or LSR polypeptides.

According to an additional aspect of the present invention the therapeutic agents can be used to prevent pathologic inhibition of T cell activity, such as that directed against cancer cells or chronic infections; and/or prevent pathologic stimulation of T cell activity, such as that directed against autoantigens in autoimmune diseases. For example, these molecules can be administered to cells in culture, in vitro or ex vivo, or to human subjects, e.g., in vivo, to treat, prevent and to diagnose a variety of disorders. Preferred subjects include human patients, having disorders mediated by cells expressing the LY6G6F, VSIG10, TMEM25 and/or LSR protein, and cells that possess LY6G6F, VSIG10, TMEM25 and/or LSR activity.

According to an additional aspect of the present invention the therapeutic agents can be used to inhibit T cell activation, as can be manifested for example by T cell proliferation and cytokine secretion.

According to an additional aspect of the present invention the therapeutic agents can be used to elicit in vivo or in vitro one or more of the following biological activities: to inhibit

the growth of and/or kill a cell expressing LY6G6F, VSIG10, TMEM25 and/or LSR; to mediate phagocytosis or ADCC of a cell expressing LY6G6F, VSIG10, TMEM25 and/or LSR in the presence of human effector cells, or to block LY6G6F, VSIG10, TMEM25 and/or LSR ligand binding to LY6G6F, VSIG10, TMEM25 and/or LSR, respectively.

Thus, according to an additional aspect of the present invention there is provided a method of treating immune related disorders as recited herein, and/or autoimmune disorders as recited herein, and/or infectious disorders as recited herein, and/or cancer as recited herein, and/or for blocking or promoting immune stimulation mediated by the LY6G6F, VSIG10, TMEM25 and/or LSR polypeptide in a subject by administering to a subject in need thereof an effective amount of any one of the therapeutic agents and/or a pharmaceutical composition comprising any of the therapeutic agents and further comprising a pharmaceutically acceptable diluent or carrier.

The subject according to the present invention is a mammal, preferably a human which is diagnosed with one of the disease, disorder or conditions described hereinabove, or alternatively is predisposed to at least one type of cancer and/or infectious disorders, and/or immune related disorder.

As used herein the term "treating" refers to preventing, delaying the onset of, curing, reversing, attenuating, alleviating, minimizing, suppressing or halting the deleterious effects of the above-described diseases, disorders or conditions. It also includes managing the disease as described above. By "manage" it is meant reducing the severity of the disease, reducing the frequency of episodes of the disease, reducing the duration of such episodes, reducing the severity of such episodes and the like.

Treating, according to the present invention, can be effected by specifically upregulating the expression of at least one of the polypeptides of the present invention in the subject.

It will be appreciated that treatment of the above-described diseases according to the present invention may be combined with other treatment methods known in the art (i.e., combination therapy). Thus the therapeutic agents and/or a pharmaceutical composition comprising same, as recited herein, according to at least some embodiments of the present invention can also be used in combination with one or more of the following agents to regulate an immune response: soluble gp39 (also known as CD40 ligand (CD40L), CD154, T-BAM, TRAP), soluble CD29, soluble CD40, soluble CD80 (e.g. ATCC 68627), soluble CD86, soluble CD28 (e.g. 68628), soluble CD56, soluble Thy-1, soluble CD3, soluble TCR, soluble VLA-4, soluble VCAM-1, soluble LECAM-1, soluble ELAM-1, soluble CD44, antibodies reactive with gp39 (e.g. ATCC HB-10916, ATCC HB-12055 and ATCC HB-12056), antibodies reactive with CD40 (e.g. ATCC HB-9110), antibodies reactive with B7 (e.g. ATCC HB-253, ATCC CRL-2223, ATCC CRL-2226, ATCC HB-301, ATCC HB-11341, etc), antibodies reactive with CD28 (e.g. ATCC HB-11944 or mAb 9.3), antibodies reactive with LFA-1 (e.g. ATCC HB-9579 and ATCC TIB-213), antibodies reactive with LFA-2, antibodies reactive with IL-2, antibodies reactive with IL-12, antibodies reactive with IFN-gamma, antibodies reactive with CD2, antibodies reactive with CD48, antibodies reactive with any ICAM (e.g., ICAM-1 (ATCC CRL-2252), ICAM-2 and ICAM-3), antibodies reactive with CTLA4 (e.g. ATCC HB-304), antibodies reactive with Thy-1, antibodies reactive with CD56, antibodies reactive with CD3, antibodies reactive with CD29, antibodies reactive with TCR, antibodies reactive with VLA-4, antibodies reactive with VCAM-1, antibodies reactive with LECAM-1, antibodies reactive with ELAM-1, antibodies reactive with CD44; L104EA29YIg,

CD80 monoclonal antibodies (mAbs), CD86 mAbs, gp39 mAbs, CD40 mAbs, CD28 mAbs; anti-LFA1 mAbs, antibodies or other agents targeting mechanisms of the immune system such as CD52 (alemtuzumab), CD25 (daclizumab), VLA-4 (natalizumab), CD20 (rituximab), IL2R (daclizumab) and MS4A1 (ocrelizumab); novel oral immunomodulating agents have shown to prevent lymphocyte recirculation from lymphoid organs such as fingolimod (FTY720) or leading to lymphocyte depletion such as mylinax (oral cladribine) or teriflunomide; and agents that prevent immunoreactivation such as panaclar (dimethyl fumarate BG-12) or laquinimod (ABR216062). Other combinations will be readily appreciated and understood by persons skilled in the art. In some embodiments, the therapeutic agents can be used to attenuate or reverse the activity of a pro-inflammatory drug, and/or limit the adverse effects of such drugs.

As persons skilled in the art will readily understand, the combination can include the therapeutic agents and/or a pharmaceutical composition comprising same, according to at least some embodiments of the invention and one other immunosuppressive agent; the therapeutic agents and/or a pharmaceutical composition comprising same, as recited herein, with two other immunosuppressive agents, the therapeutic agents and/or a pharmaceutical composition comprising same, as recited herein, with three other immunosuppressive agents, etc. The determination of the optimal combination and dosages can be determined and optimized using methods well known in the art.

The therapeutic agent according to the present invention and one or more other therapeutic agents can be administered in either order or simultaneously. The other therapeutic agents are for example, a cytotoxic agent, a radiotoxic agent or an immunosuppressive agent. The composition can be linked to the agent (as an immunocomplex) or can be administered separately from the agent. In the latter case (separate administration), the composition can be administered before, after or concurrently with the agent or can be co-administered with other known therapies, e.g., an anti-cancer therapy, e.g., radiation. Such therapeutic agents include, among others, anti-neoplastic agents such as doxorubicin (adriamycin), cisplatin bleomycin sulfate, carmustine, chlorambucil, and cyclophosphamide hydroxyurea which, by themselves, are only effective at levels which are toxic or subtoxic to a patient. Cisplatin is intravenously administered as a 100 mg/dose once every four weeks and adriamycin is intravenously administered as a 60-75 mg/ml dose once every 21 days.

Co-administration of the human anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR antibodies, or antigen binding fragments thereof, according to at least some embodiments of the present invention with chemotherapeutic agents provides two anti-cancer agents which operate via different mechanisms which yield a cytotoxic effect to human tumor cells. Such co-administration can solve problems due to development of resistance to drugs or a change in the antigenicity of the tumor cells which would render them unreactive with the antibody. Target-specific effector cells, e.g., effector cells linked to compositions (e.g., human antibodies, multispecific and bispecific molecules) according to at least some embodiments of the invention can also be used as therapeutic agents. Effector cells for targeting can be human leukocytes such as macrophages, neutrophils or monocytes. Other cells include eosinophils, natural killer cells and other IgG- or IgA-receptor bearing cells. If desired, effector cells can be obtained from the subject to be treated. The target-specific effector cells can be administered as a suspension of cells in a physiologically acceptable solution. The number of cells administered can be in the order of 10-8

to 10-9 but will vary depending on the therapeutic purpose. In general, the amount will be sufficient to obtain localization at the target cell, e.g., a tumor cell expressing LY6G6F, VSIG10, TMEM25 and/or LSR proteins, and to effect cell killing by, e.g., phagocytosis. Routes of administration can also vary.

Therapy with target-specific effector cells can be performed in conjunction with other techniques for removal of targeted cells. For example, anti-tumor therapy using the compositions (e.g., human antibodies, multispecific and bispecific molecules) according to at least some embodiments of the invention and/or effector cells armed with these compositions can be used in conjunction with chemotherapy. Additionally, combination immunotherapy may be used to direct two distinct cytotoxic effector populations toward tumor cell rejection. For example, anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR antibodies linked to anti-Fc-gamma RI or anti-CD3 may be used in conjunction with IgG- or IgA-receptor specific binding agents.

Bispecific and multispecific molecules according to at least some embodiments of the invention can also be used to modulate Fc-gammaR or Fc-gammaR levels on effector cells, such as by capping and elimination of receptors on the cell surface. Mixtures of anti-Fc receptors can also be used for this purpose.

The invention also encompasses the use of the compositions according to at least some embodiments of the invention in combination with other pharmaceutical agents to treat immune system diseases. For example, autoimmune disease may be treated with molecules according to at least some embodiments of the invention in conjunction with, but not limited to, immunosuppressants such as corticosteroids, cyclosporin, cyclophosphamide, prednisone, azathioprine, methotrexate, rapamycin, tacrolimus, biological agents such as TNF-alpha blockers or antagonists, or any other biological agent targeting any inflammatory cytokine, nonsteroidal anti-inflammatory drugs/Cox-2 inhibitors, hydroxychloroquine, sulphasalazopyrine, gold salts, etanercept, infliximab, mycophenolate mofetil, basiliximab, atacept, rituximab, cytoxan, interferon beta-1a, interferon beta-1b, glatiramer acetate, mitoxantrone hydrochloride, anakinra and/or other biologics and/or intravenous immunoglobulin (IVIG). Non-limiting examples of such known therapeutics include interferons, such as IFN-beta-1a (REBIF®. AVONEX® and CINNOVEX®) and IFN-beta-1b (BETASERON®, EXTAVIA®, BETAFERON®, ZIFERON®); glatiramer acetate (COPAXONE®), a polypeptide; natalizumab (TYSABRI®); and mitoxantrone (NOVANTRONE®), a cytotoxic agent.

Thus, treatment of multiple sclerosis using the agents according to at least some embodiments of the present invention may be combined with, for example, any known therapeutic agent or method for treating multiple sclerosis. Non-limiting examples of such known therapeutic agent or method for treating multiple sclerosis include interferon class, IFN-beta-1a (REBIF®. AVONEX® and CINNOVEX®) and IFN-beta-1b (BETASERON®, EXTAVIA®, BETAFERON®, ZIFERON®); glatiramer acetate (COPAXONE®), a polypeptide; natalizumab (TYSABRI®); and mitoxantrone (NOVANTRONE®), a cytotoxic agent, Fampridine (AMPYRA®). Other drugs include corticosteroids, methotrexate, cyclophosphamide, azathioprine, and intravenous immunoglobulin (IVIG), inosine, Ocrelizumab (R1594), Mylinax (Caldribine), alemtuzumab (Campath), daclizumab (Zenapax), Panaclar/dimethyl fumarate (BG-12), Teriflunomide (HMR1726), fingolimod (FTY720), laquinimod (ABR216062), as well as Haematopoietic stem cell transplantation, Neurovax, Rituximab (Rituxan) BCG vaccine,

low dose naltrexone, helminthic therapy, angioplasty, venous stents, and alternative therapy, such as vitamin D, polyunsaturated fats, medical marijuana.

Thus, treatment of rheumatoid arthritis, using the agents according to at least some embodiments of the present invention may be combined with, for example, any known therapeutic agent or method for treating rheumatoid arthritis. Non-limiting examples of such known therapeutic agents or methods for treating rheumatoid arthritis include glucocorticoids, nonsteroidal anti-inflammatory drug (NSAID) such as salicylates, or cyclooxygenase-2 inhibitors, ibuprofen and naproxen, diclofenac, indomethacin, etodolac Disease-modifying antirheumatic drugs (DMARDs)-Oral DMARDs: Auranofin (Ridaura), Azathioprine (Imuran), Cyclosporine (Sandimmune, Gengraf, Neoral, generic), D-Penicillamine (Cuprimine), Hydroxychloroquine (Plaquenil), IM gold Gold sodium thiomalate (Myochrysine) Aurothioglucose (Solganal), Leflunomide (Arava), Methotrexate (Rheumatrex), Minocycline (Minocin), Staphylococcal protein A immunoadsorption (Prosorba column), Sulfasalazine (Azulfidine). Biologic DMARDs: TNF- α blockers including Adalimumab (Humira), Etanercept (Enbrel), Infliximab (Remicade), golimumab (Simponi), certolizumab pegol (Cimzia), and other Biological DMARDs, such as Anakinra (Kineret), Rituximab (Rituxan), Tocilizumab (Actemra), CD28 inhibitor including Abatacept (Orencia) and Belatacept.

Thus, treatment of IBD, using the agents according to at least some embodiments of the present invention may be combined with, for example, any known therapeutic agent or method for treating IBD. Non-limiting examples of such known therapeutic agents or methods for treating IBD include immunosuppression to control the symptom, such as prednisone, Mesalazine (including Asacol, Pentasa, Lialda, Aspiro), azathioprine (Imuran), methotrexate, or 6-mercaptopurine, steroids, Ondansetron, TNF- α blockers (including infliximab, adalimumab golimumab, certolizumab pegol), Orencia (abatacept), ustekinumab (Stelara®), Briakinumab (ABT-874), Certolizumab pegol (Cimzia®), ITF2357 (givinostat), Natalizumab (Tysabri), Finategrast (SB-683699), Remicade (infliximab), vedolizumab (MLN0002), other drugs including GSK1605786 CCX282-B (Traficet-EN), AJM300, Stelara (ustekinumab), Semapimod (CNI-1493) tasocitinib (CP-690550), LMW Heparin MMX, Budesonide MMX, Simponi (golimumab), MultiStem®, Gardasil HPV vaccine, Epaxal Berna (viroosomal hepatitis A vaccine), surgery, such as bowel resection, stricturoplasty or a temporary or permanent colostomy or ileostomy; antifungal drugs such as nystatin (a broad spectrum gut antifungal) and either itraconazole (Sporanox) or fluconazole (Diflucan); alternative medicine, prebiotics and probiotics, *cannabis*, Helminthic therapy or ova of the *Trichuris suis* helminth.

Thus, treatment of psoriasis, using the agents according to at least some embodiments of the present invention may be combined with, for example, any known therapeutic agent or method for treating psoriasis. Non-limiting examples of such known therapeutics for treating psoriasis include topical agents, typically used for mild disease, phototherapy for moderate disease, and systemic agents for severe disease. Non-limiting examples of topical agents: bath solutions and moisturizers, mineral oil, and petroleum jelly; ointment and creams containing coal tar, dithranol (anthralin), corticosteroids like desoximetasone (Topicort), Betamethasone, fluocinonide, vitamin D3 analogues (for example, calcipotriol), and retinoids. Non-limiting examples of phototherapy: sunlight; wavelengths of 311-313 nm, psoralen and ultraviolet A phototherapy (PUVA). Non-limiting examples of systemic agents: Biologics, such as interleukin antagonists, TNF- α

blockers including antibodies such as infliximab (Remicade), adalimumab (Humira), golimumab, certolizumab pegol, and recombinant TNF- α decoy receptor, etanercept (Enbrel); drugs that target T cells, such as efalizumab (Xannelim/Raptiva), alefacept (Ameviv), dendritic cells such Efalizumab; monoclonal antibodies (MAbs) targeting cytokines, including anti-IL-12/IL-23 (ustekinumab (brand name Stelara)) and anti-Interleukin-17; Briakinumab (ABT-874); small molecules, including but not limited to ISA247; Immunosuppressants, such as methotrexate, cyclosporine; vitamin A and retinoids (synthetic forms of vitamin A); and alternative therapy, such as changes in diet and lifestyle, fasting periods, low energy diets and vegetarian diets, diets supplemented with fish oil rich in Vitamin A and Vitamin D (such as cod liver oil), Fish oils rich in the two omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and contain Vitamin E. Ichthyotherapy, Hypnotherapy, *cannabis*.

Thus, treatment of type 1 diabetes, using the agents according to at least some embodiments of the present invention may be combined with, for example, any known therapeutic agent or method for treating type 1 diabetes. Non-limiting examples of such known therapeutics for treating type 1 diabetes include insulin, insulin analogs, islet transplantation, stem cell therapy including PROCHYMAL®, non-insulin therapies such as il-1 beta inhibitors including Anakinra (Kineret®), Abatacept (Orencia®), Diamyd, alefacept (Ameviv®), Otelixizumab, DiaPep277 (Hsp60 derived peptide), Alpha 1-Antitrypsin, Prednisone, azathioprine, Cyclosporin, E1-INT (an injectable islet neogenesis therapy comprising an epidermal growth factor analog and a gastrin analog), statins including Zocor®, Simlup®, Simcard®, Simvacor®, Sitagliptin (dipeptidyl peptidase (DPP-4) inhibitor), Anti-CD3 mAb (e.g., Teplizumab); CTLA4-Ig (abatacept), Anti IL-1 Beta (Canakinumab), Anti-CD20 mAb (e.g., rituximab).

Thus, treatment of uveitis, using the agents according to at least some embodiments of the present invention may be combined with, for example, any known therapeutic agent or method for treating uveitis. Non-limiting examples of such known therapeutics for treating uveitis include corticosteroids, topical cycloplegics, such as atropine or homatropine, or injection of PSTTA (posterior subtenon triamcinolone acetate), antimetabolite medications, such as methotrexate, TNF- α blockers (including infliximab, adalimumab, etanercept, golimumab, certolizumab pegol).

Thus, treatment for Sjogren's syndrome, using the agents according to at least some embodiments of the present invention may be combined with, for example, any known therapeutic agent or method for treating for Sjogren's syndrome. Non-limiting examples of such known therapeutics for treating for Sjogren's syndrome include Cyclosporine, pilocarpine (Salagen) and cevimeline (Evinoxac), Hydroxychloroquine (Plaquenil), cortisone (prednisone and others) and/or azathioprine (Imuran) or cyclophosphamide (Cytosan), Dexamethasone, Thalidomide, Dehydroepiandrosterone, NGX267, Rebamipide, FID 114657, Etanercept, Raptiva, Belimumab, MabThera (rituximab); Anakinra, intravenous immune globulin (IVIG), Allogeneic Mesenchymal Stem Cells (AlloMSC), Automatic neuro-electrostimulation by "Saliwell Crown".

Thus, treatment for systemic lupus erythematosus, using the agents according to at least some embodiments of the present invention may be combined with, for example, any known therapeutic agent or method for treating for systemic lupus erythematosus. Non-limiting examples of such known therapeutics for treating for systemic lupus erythematosus include corticosteroids and Disease-modifying antirheumatic

drugs (DMARDs), commonly anti-malarial drugs such as plaquenil and immunosuppressants (e.g. methotrexate and azathioprine) Hydroxychloroquine, cytotoxic drugs (e.g., cyclophosphamide and mycophenolate), Hydroxychloroquine (HCQ), Benlysta (belimumab), nonsteroidal anti-inflammatory drugs, Prednisone, Cellcept, Prograf, Atacicept, Lupuzor, Intravenous Immunoglobulins (IVIGs), CellCept (mycophenolate mofetil), Orencia, CTLA4-IgG4m (RG2077), rituximab, Ocrelizumab, Epratuzumab, CNTO 136, Sifalimumab (MEDI-545), A-623 (formerly AMG 623), AMG 557, Rontalizumab, paquinimod (ABR-215757), LY2127399, CEP-33457, Dehydroepiandrosterone, Levothyroxine, abetimus sodium (LIP 394), Memantine, Opiates, Rapamycin, Renal transplantation, stem cell transplantation.

The therapeutic agents and/or a pharmaceutical composition comprising same, as recited herein, according to at least some embodiments of the invention, may be administered as the sole active ingredient or together with other drugs in immunomodulating regimens or other anti-inflammatory agents e.g. for the treatment or prevention of allo- or xenograft acute or chronic rejection or inflammatory or autoimmune disorders, or to induce tolerance.

For example, it may be used in combination with a calcineurin inhibitor, e.g. cyclosporin A or FK506; an immunosuppressive macrolide, e.g. rapamycin or a derivative thereof; e.g. 40-O-(2-hydroxy)ethyl-rapamycin, a lymphocyte homing agent, e.g. FTY720 or an analog thereof, corticosteroids; cyclophosphamide; azathioprene; methotrexate; leflunomide or an analog thereof; mizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualine or an analog thereof; immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD 11a/CD18, CD7, CD25, CD 27, B7, CD40, CD45, CD58, CD 137, ICOS, CD150 (SLAM), OX40, 4-1BB or their ligands; or other immunomodulatory compounds, e.g. CTLA4-Ig (abatacept, ORENCIA® or belatacept), CD28-Ig, B7-H4-Ig, or other costimulatory agents, or adhesion molecule inhibitors, e.g. mAbs or low molecular weight inhibitors including LFA-1 antagonists, Selectin antagonists and VLA-4 antagonists.

Where the therapeutic agents and/or a pharmaceutical composition comprising same, as recited herein, according to at least some embodiments of the invention are administered in conjunction with other immunosuppressive/immunomodulatory or anti-inflammatory therapy, e.g. as herein above specified, dosages of the co-administered immunosuppressant, immunomodulatory or anti-inflammatory compound will of course vary depending on the type of co-drug employed, e.g. whether it is a steroid or a cyclosporin, on the specific drug employed, on the condition being treated and so forth.

Treatment of malignancies using the agents of the present invention may be combined with other treatment methods known in the art, one or more of, for example, radiation therapy, antibody therapy, chemotherapy, photodynamic therapy, surgery or in combination therapy with conventional drugs, such as immunosuppressants or cytotoxic drugs.

A therapeutic agent or pharmaceutical composition according to at least some embodiments of the present invention may also be administered in conjunction with other compounds or immunotherapies. For example, the combination therapy can include a compound of the present invention combined with at least one other therapeutic or immune modulatory agent, or immunostimulatory strategy, including, but not limited to, tumor vaccines, adoptive T cell therapy, Treg depletion, antibodies (e.g. bevacizumab, erbitux), pep-

tides, pepti-bodies, small molecules, chemotherapeutic agents such as cytotoxic and cytostatic agents (e.g. paclitaxel, cisplatin, vinorelbine, docetaxel, gemcitabine, temozolomide, irinotecan, 5FU, carboplatin), immunological modifiers such as interferons and interleukins, immunostimulatory antibodies, growth hormones or other cytokines, folic acid, vitamins, minerals, aromatase inhibitors, RNAi, Histone Deacetylase Inhibitors, proteasome inhibitors, and so forth.

According to at least some embodiments of the present invention, there is provided use of a combination of the therapeutic agents and/or a pharmaceutical composition comprising same, as recited herein, and a known therapeutic agent effective for treating infection.

The therapeutic agents and/or a pharmaceutical composition comprising same, as recited herein, can be administered in combination with one or more additional therapeutic agents used for treatment of bacterial infections, including, but not limited to, antibiotics including Aminoglycosides, Carbapenems, Cephalosporins, Macrolides, Lincosamides, Nitrofurans, penicillins, Polypeptides, Quinolones, Sulfonamides, Tetracyclines, drugs against mycobacteria including but not limited to Clofazimine, Cycloserine, Cycloserine, Rifabutin, Rifapentine, Streptomycin and other antibacterial drugs such as Chloramphenicol, Fosfomycin, Metronidazole, Mupirocin, and Tinidazole.

The therapeutic agents and/or a pharmaceutical composition comprising same, as recited herein, can be administered in combination with one or more additional therapeutic agents used for treatment of viral infections, including, but not limited to, antiviral drugs such as oseltamivir (brand name Tamiflu) and zanamivir (brand name Relenza) Arbidol—adamantane derivatives (Amantadine, Rimantadine)—neuraminidase inhibitors (Oseltamivir, Laninamivir, Peramivir, Zanamivir) nucleotide analog reverse transcriptase inhibitor including Purine analogue guanine (Aciclovir#/Valacyclovir, Ganciclovir/Valganciclovir, Penciclovir/Famciclovir) and adenine (Vidarabine), Pyrimidine analogue, uridine (Idoxuridine, Trifluridine, Edoxudine), thymine (Brivudine), cytosine (Cytarabine); Foscarnet; Nucleoside analogues/NRTIs: Entecavir, Lamivudine, Telbivudine, Clevudine; Nucleotide analogues/NtRTIs: Adefovir, Tenofovir; Nucleic acid inhibitors such as Cidofovir; Interferon/Interferon alfa-2b, Peginterferon alfa-2a; Ribavirin#/Taribavirin; antiretroviral drugs including zidovudine, lamivudine, abacavir, lopinavir, ritonavir, tenofovir/emtricitabine, efavirenz each of them alone or a various combinations, gp41 (Enfuvirtide), Raltegravir, protease inhibitors such as Fosamprenavir, Lopinavir and Atazanavir, Methisazone, Docosanol, Fomivirsin, Tromantadine.

The therapeutic agents and/or a pharmaceutical composition comprising same, as recited herein, can be administered in combination with one or more additional therapeutic agents used for treatment of fungal infections, including, but not limited to, antifungal drugs of the Polyene antifungals, Imidazole, triazole, and thiazole antifungals, Allylamines, Echinocandins or other anti fungal drugs.

Alternatively or additionally, an upregulating method may optionally be effected by specifically upregulating the amount (optionally expression) in the subject of at least one of the polypeptides of the present invention or active portions thereof.

As is mentioned hereinabove and in the Examples section which follows, the biomolecular sequences of this aspect of the present invention may be used as valuable therapeutic tools in the treatment of diseases, disorders or conditions in which altered activity or expression of the wild-type gene product (known protein) is known to contribute to disease,

disorder or condition onset or progression. For example, in case a disease is caused by overexpression of a membrane bound-receptor, a soluble variant thereof may be used as an antagonist which competes with the receptor for binding the ligand, to thereby terminate signaling from the receptor.

According to at least some embodiments, immune cells, preferably T cells, can be contacted in vivo or ex vivo with the therapeutic agents to modulate immune responses. The T cells contacted with the therapeutic agents can be any cell which expresses the T cell receptor, including α/β and γ/δ T cell receptors. T-cells include all cells which express CD3, including T-cell subsets which also express CD4 and CD8. T-cells include both naive and memory cells and effector cells such as CTL. T-cells also include cells such as Th1, Tc1, Th2, Tc2, Th3, Th17, Th22, Treg, and Tr1 cells. T-cells also include NKT-cells and similar unique classes of the T-cell lineage.

Inhibition of Epitope Spreading

Epitope spreading refers to the ability of B and T cell immune response to diversify both at the level of specificity, from a single determinant to many sites on an auto antigen, and at the level of V gene usage (Monneaux, F. et al., *Arthritis & Rheumatism*, 46(6): 1430-1438 (2002). Epitope spreading is not restricted to systemic autoimmune disease. It has been described in T cell dependent organ specific diseases such as Diabetes mellitus type 1 and multiple sclerosis in humans, and EAE induced experimental animals with a variety of myelin proteins.

Epitope spreading involves the acquired recognition of new epitopes in the same self molecule as well as epitopes residing in proteins that are associated in the same macromolecular complex. Epitope spreading can be assessed by measuring delayed-type hypersensitivity (DTH) responses, methods of which are known in the art.

One embodiment provides a method for inhibiting or reducing epitope spreading in a subject by administering to the subject an effective amount of the therapeutic agents. In a further embodiment any one of the therapeutic agents inhibits epitope spreading in individuals with multiple sclerosis. Preferably, the therapeutic agents inhibit or block multiple points of the inflammation pathway.

Yet another embodiment provides a method for inhibiting or reducing epitope spreading in subjects with multiple sclerosis by administering to a subject an effective amount of the therapeutic agents to inhibit or reduce differentiation of, proliferation of, activity of, and/or cytokine production and/or secretion by Th1, Th17, Th22, and/or other cells that secrete, or cause other cells to secrete, inflammatory molecules, including, but not limited to, IL-1 beta, TNF-alpha, TGF-beta, IFN-gamma, IL-17, IL-6, IL-23, IL-22, IL-21, and MMPs.

Use of the Therapeutic Agents According to at Least Some Embodiments of the Invention as Adjuvant for Cancer Vaccination:

Immunization against tumor-associated antigens (TAAs) is a promising approach for cancer therapy and prevention, but it faces several challenges and limitations, such as tolerance mechanisms associated with self-antigens expressed by the tumor cells. Costimulatory molecules such as B7.1 (CD80) and B7.2 (CD86) have improved the efficacy of gene-based and cell-based vaccines in animal models and are under investigation as adjuvant in clinical trials. This adjuvant activity can be achieved either by enhancing the costimulatory signal or by blocking inhibitory signal that is transmitted by negative costimulators expressed by tumor cells (Neighbors et al., 2008 *J Immunother.*; 31(7):644-55). According to at least some embodiments of the invention, any one of

LY6G6F, VSIG10, TMEM25 and/or LSR secreted or soluble form or ECD and/or variants, and/or orthologs, and/or conjugates thereof, and/or a polyclonal or monoclonal antibody and/or antigen binding fragments and/or conjugates containing same, and/or alternative scaffolds, specific to any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins, can be used as adjuvant for cancer vaccination. According to at least some embodiments, the invention provides methods for improving immunization against TAAs, comprising administering to a patient an effective amount of any one of LY6G6F, VSIG10, TMEM25 and/or LSR secreted or soluble form or ECD and/or variants, and/or orthologs, and/or conjugates thereof, and/or a polyclonal or monoclonal antibody and/or antigen binding fragments and/or conjugates containing same, and/or alternative scaffolds, specific to any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins.

Use of the Therapeutic Agents According to at Least Some Embodiments of the Invention for Adoptive Immunotherapy:

One of the cardinal features of some models of tolerance is that once the tolerance state has been established, it can be perpetuated to naive recipients by the adoptive transfer of donor-specific regulatory cells. Such adoptive transfer studies have also addressed the capacity of T-cell subpopulations and non-T cells to transfer tolerance. Such tolerance can be induced by blocking costimulation or upon engagement of a co-inhibitory B7 with its counter receptor. This approach, that have been successfully applied in animals and is evaluated in clinical trials in humans, (Scalapino K J and Daikh D I. *PLoS One*. 2009; 4(6):e6031; Riley et al., *Immunity*. 2009; 30(5): 656-665) provides a promising treatment option for autoimmune disorders and transplantation. According to at least some embodiments of the invention, LY6G6F, VSIG10, TMEM25 and/or LSR secreted or soluble form or ECD and/or variants, and/or orthologs, and/or conjugates thereof, and/or a polyclonal or monoclonal antibody and/or antigen binding fragments and/or conjugates containing same, and/or alternative scaffolds, specific to any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins are used for adoptive immunotherapy. Thus, according to at least some embodiments, the invention provides methods for in vivo or ex vivo tolerance induction, comprising administering effective amount of LY6G6F, VSIG10, TMEM25 and/or LSR secreted or soluble form or ECD and/or variants, and/or orthologs, and/or conjugates thereof, and/or a polyclonal or monoclonal antibody or and/or antigen binding fragments and/or conjugates containing same, and/or alternative scaffolds, specific to any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins, to a patient or to leukocytes isolated from the patient, in order to induce differentiation of tolerogenic regulatory cells; followed by ex-vivo enrichment and expansion of said cells and reinfusion of the tolerogenic regulatory cells to said patient.

Alternatively, immune responses can be enhanced in a patient by removing immune cells from the patient, contacting immune cells in vitro with an agent that inhibits LY6G6F, VSIG10, TMEM25 and/or LSR activity, and/or which inhibits the interaction of LY6G6F, VSIG10, TMEM25 and/or LSR with their natural binding partners, and reintroducing the in vitro stimulated immune cells into the patient. In another embodiment, a method of modulating immune responses involves isolating immune cells from a patient, transfecting them with a nucleic acid molecule encoding a form of LY6G6F, VSIG10, TMEM25 and/or LSR, such that the cells express all or a portion of the LY6G6F, VSIG10, TMEM25 and/or LSR polypeptide according to various embodiments of the present invention on their surface, and reintroducing

the transfected cells into the patient. The transfected cells have the capacity to modulate immune responses in the patient.

Use of the Therapeutic Agents According to at Least Some Embodiments of the Invention for Immunoenhancement

1. Treatment of Cancer

The therapeutic agents provided herein are generally useful in vivo and ex vivo as immune response-stimulating therapeutics. In general, the disclosed therapeutic agent compositions are useful for treating a subject having or being predisposed to any disease or disorder to which the subject's immune system mounts an immune response. The ability of therapeutic agents to modulate LY6G6F, VSIG10, TMEM25 and/or LSR immune signals enable a more robust immune response to be possible. The therapeutic agents according to at least some embodiments of the invention are useful to stimulate or enhance immune responses involving immune cells, such as T cells.

The therapeutic agents according to at least some embodiments of the invention are useful for stimulating or enhancing an immune response in host for treating cancer by administering to a subject an amount of a therapeutic agent effective to stimulate T cells in the subject.

2. Use of the Therapeutic Agents in Vaccines

The therapeutic agents according to at least some embodiments of the invention, are administered alone or in combination with any other suitable treatment. In one embodiment the therapeutic agents can be administered in conjunction with, or as a component of a vaccine composition as described above. The therapeutic agents according to at least some embodiments of the invention can be administered prior to, concurrently with, or after the administration of a vaccine. In one embodiment the therapeutic agents is administered at the same time as administration of a vaccine.

Pharmaceutical Compositions

In another aspect, the present invention provides a composition, e.g., a pharmaceutical composition, containing one or a combination of the therapeutic agent, according to at least some embodiments of the invention.

Thus, the present invention features a pharmaceutical composition comprising a therapeutically effective amount of a therapeutic agent according to at least some embodiments of the present invention.

The pharmaceutical composition according to at least some embodiments of the present invention is further preferably used for the treatment of cancer, wherein the cancer may be non-metastatic, invasive or metastatic, treatment of immune related disorder and/or infectious disorder.

"Treatment" refers to both therapeutic treatment and prophylactic or preventative measures. Those in need of treatment include those already with the disorder as well as those in which the disorder is to be prevented. Hence, the mammal to be treated herein may have been diagnosed as having the disorder or may be predisposed or susceptible to the disorder. "Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, etc. Preferably, the mammal is human.

The term "therapeutically effective amount" refers to an amount of agent according to the present invention that is effective to treat a disease or disorder in a mammal.

The therapeutic agents of the present invention can be provided to the subject alone, or as part of a pharmaceutical composition where they are mixed with a pharmaceutically acceptable carrier.

Pharmaceutical compositions according to at least some embodiments of the invention also can be administered in

combination therapy, i.e., combined with other agents. For example, the combination therapy can include an anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR antibody or LY6G6F, VSIG10, TMEM25 and/or LSR modulating agent according to at least some embodiments of the present invention, such as a soluble polypeptide conjugate containing the ectodomain of the LY6G6F, VSIG10, TMEM25 and/or LSR antigen or a small molecule such as a peptide, ribozyme, aptamer, siRNA, or other drug that binds LY6G6F, VSIG10, TMEM25 and/or LSR, combined with at least one other therapeutic or immune modulatory agent.

A composition is said to be a "pharmaceutical acceptable carrier" if its administration can be tolerated by a recipient patient. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Preferably, the carrier is suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (e.g., by injection or infusion).

Such compositions include sterile water, buffered saline (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength and optionally additives such as detergents and solubilizing agents (e.g., Polysorbate 20, Polysorbate 80), antioxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimersol, benzyl alcohol) and bulking substances (e.g., lactose, manitol). Non-aqueous solvents or vehicles may also be used as detailed below.

Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions according to at least some embodiments of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. Depending on the route of administration, the active compound, i.e., soluble polypeptide conjugate containing the ectodomain of the LY6G6F, VSIG10, TMEM25 and/or LSR antigen, monoclonal or polyclonal antibodies and antigen binding fragments and conjugates containing same, and/or alternative scaffolds, that specifically bind any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins, or bispecific molecule, may be coated in a material to protect the compound from the action of acids and other natural conditions that may inactivate the compound. The pharmaceutical compounds according to at least some embodiments of the invention may include one or more pharmaceutically acceptable salts. A "pharmaceutically acceptable salt" refers to a salt that retains the desired biological activity of the parent compound and does not impart any undesired toxicological effects (see e.g., Berge, S. M., et al. (1977) J. Pharm. Sci. 66: 1-19). Examples of such salts include acid addition salts and base addition salts. Acid addition salts include those derived from nontoxic inorganic acids, such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, phosphorous and the like, as well as from nontoxic organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanic acids, hydroxy alkanic acids, aromatic acids, aliphatic and aromatic sulfonic acids and the like. Base addition salts include those derived from alkaline earth metals, such as sodium, potassium, magnesium, calcium and the like, as well as from nontoxic organic amines, such as N,N'-dibenzylethylenediamine, N-methylglucamine, chlorprocaine, choline, diethanolamine, ethylenediamine, procaine and the like.

A pharmaceutical composition according to at least some embodiments of the invention also may include a pharmaceutically acceptable anti-oxidant. Examples of pharmaceutically acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of presence of microorganisms may be ensured both by sterilization procedures, supra, and by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions according to at least some embodiments of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin. Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by sterilization microfiltration. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying (lyophilization) that yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enu-

merated above, as required, followed by sterilization microfiltration. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying (lyophilization) that yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the subject being treated, and the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the composition which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 0.01 percent to about ninety-nine percent of active ingredient, preferably from about 0.1 percent to about 70 percent, most preferably from about 1 percent to about 30 percent of active ingredient in combination with a pharmaceutically acceptable carrier.

Dosage regimens are adjusted to provide the optimum desired response (e.g., a therapeutic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms according to at least some embodiments of the invention are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

For administration of the antibody, the dosage ranges from about 0.0001 to 100 mg/kg, and more usually 0.01 to 5 mg/kg, of the host body weight. For example dosages can be 0.3 mg/kg body weight, 1 mg/kg body weight, 3 mg/kg body weight, 5 mg/kg body weight or 10 mg/kg body weight or within the range of 1-10 mg/kg. An exemplary treatment regime entails administration once per week, once every two weeks, once every three weeks, once every four weeks, once a month, once every 3 months or once every three to 6 months. Preferred dosage regimens for an antibody according to at least some embodiments of the invention include 1 mg/kg body weight or 3 mg/kg body weight via intravenous administration, with the antibody being given using one of the following dosing schedules: (i) every four weeks for six dosages, then every three months; (ii) every three weeks; (iii) 3 mg/kg body weight once followed by 1 mg/kg body weight every three weeks.

For fusion proteins as described herein, optionally a similar dosage regimen is followed; alternatively, the fusion proteins may optionally be administered in an amount between 0.0001 to 100 mg/kg weight of the patient/day, preferably between 0.001 to 10.0 mg/kg/day, according to any suitable timing regimen. A therapeutic composition according to at least some embodiments of the invention can be administered, for example, three times a day, twice a day, once a day, three

times weekly, twice weekly or once weekly, once every two weeks or 3, 4, 5, 6, 7 or 8 weeks. Moreover, the composition can be administered over a short or long period of time (e.g., 1 week, 1 month, 1 year, 5 years).

In some methods, two or more monoclonal antibodies with different binding specificities are administered simultaneously, in which case the dosage of each antibody administered falls within the ranges indicated. Antibody is usually administered on multiple occasions. Intervals between single dosages can be, for example, weekly, monthly, every three months or yearly. Intervals can also be irregular as indicated by measuring blood levels of antibody to the target antigen in the patient. In some methods, dosage is adjusted to achieve a plasma antibody concentration of about 1-1000 µg/ml and in some methods about 25-300 µg/ml.

Alternatively, therapeutic agent can be administered as a sustained release formulation, in which case less frequent administration is required. Dosage and frequency vary depending on the half-life of the therapeutic agent in the patient. In general, human antibodies show the longest half life, followed by humanized antibodies, chimeric antibodies, and nonhuman antibodies. The half-life for fusion proteins may vary widely. The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic. In prophylactic applications, a relatively low dosage is administered at relatively infrequent intervals over a long period of time. Some patients continue to receive treatment for the rest of their lives. In therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, and preferably until the patient shows partial or complete amelioration of symptoms of disease. Thereafter, the patient can be administered a prophylactic regime.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of the present invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. The selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A "therapeutically effective dosage" of LY6G6F, VSIG10, TMEM25 and/or LSR soluble protein or LY6G6F, VSIG10, TMEM25 and/or LSR ectodomain or fusion protein containing same, or an anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR antibody according to at least some embodiments of the invention preferably results in a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, an increase in lifespan, disease remission, or a prevention or reduction of impairment or disability due to the disease affliction. For example, for the treatment of LY6G6F, VSIG10, TMEM25 and/or LSR positive tumors, e.g., melanoma, cancers of liver, renal, brain, breast, colon, lung, ovary, pancreas, prostate, stomach, multiple myeloma and hematopoietic cancer, including but not limited to lymphoma (Hodgkin's and non Hodgkin's), acute and chronic lymphoblastic leukemia and acute and chronic myeloid leukemia, a "therapeutically

effective dosage" preferably inhibits cell growth or tumor growth by at least about 20%, more preferably by at least about 40%, even more preferably by at least about 60%, and still more preferably by at least about 80% relative to untreated subjects. The ability of a compound to inhibit tumor growth can be evaluated in an animal model system predictive of efficacy in human tumors. Alternatively, this property of a composition can be evaluated by examining the ability of the compound to inhibit, such inhibition in vitro by assays known to the skilled practitioner. A therapeutically effective amount of a therapeutic compound can decrease tumor size, or otherwise ameliorate symptoms in a subject.

One of ordinary skill in the art would be able to determine a therapeutically effective amount based on such factors as the subject's size, the severity of the subject's symptoms, and the particular composition or route of administration selected.

A composition of the present invention can be administered via one or more routes of administration using one or more of a variety of methods known in the art. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. Preferred routes of administration for therapeutic agents according to at least some embodiments of the invention include intravascular delivery (e.g. injection or infusion), intravenous, intramuscular, intradermal, intraperitoneal, subcutaneous, spinal, oral, enteral, rectal, pulmonary (e.g. inhalation), nasal, topical (including transdermal, buccal and sublingual), intravesical, intravitreal, intraperitoneal, vaginal, brain delivery (e.g. intra-cerebroventricular, intra-cerebral, and convection enhanced diffusion), CNS delivery (e.g. intrathecal, perispinal, and intra-spinal) or parenteral (including subcutaneous, intramuscular, intravenous and intradermal), transmucosal (e.g., sublingual administration), administration or administration via an implant, or other parenteral routes of administration, for example by injection or infusion, or other delivery routes and/or forms of administration known in the art. The phrase "parenteral administration" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion. In a specific embodiment, a protein, a therapeutic agent or a pharmaceutical composition according to at least some embodiments of the present invention can be administered intraperitoneally or intravenously.

Alternatively, an LY6G6F, VSIG10, TMEM25 and/or LSR specific antibody or other LY6G6F, VSIG10, TMEM25 and/or LSR drug or molecule and their conjugates and combinations thereof that modulates a LY6G6F, VSIG10, TMEM25 and/or LSR protein activity can be administered via a non-parenteral route, such as a topical, epidermal or mucosal route of administration, for example, intranasally, orally, vaginally, rectally, sublingually or topically.

The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. See, e.g., Sustained

and Controlled Release Drug Delivery Systems, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

Therapeutic compositions can be administered with medical devices known in the art. For example, in a preferred embodiment, a therapeutic composition according to at least some embodiments of the invention can be administered with a needles hypodermic injection device, such as the devices disclosed in U.S. Pat. Nos. 5,399,163; 5,383,851; 5,312,335; 5,064,413; 4,941,880; 4,790,824; or 4,596,556. Examples of well-known implants and modules useful in the present invention include: U.S. Pat. No. 4,487,603, which discloses an implantable micro-infusion pump for dispensing medication at a controlled rate; U.S. Pat. No. 4,486,194, which discloses a therapeutic device for administering medicaments through the skin; U.S. Pat. No. 4,447,233, which discloses a medication infusion pump for delivering medication at a precise infusion rate; U.S. Pat. No. 4,447,224, which discloses a variable flow implantable infusion apparatus for continuous drug delivery; U.S. Pat. No. 4,439,196, which discloses an osmotic drug delivery system having multi-chamber compartments; and U.S. Pat. No. 4,475,196, which discloses an osmotic drug delivery system. These patents are incorporated herein by reference. Many other such implants, delivery systems, and modules are known to those skilled in the art.

In certain embodiments, the antibodies, LY6G6F, VSIG10, TMEM25 and/or LSR soluble proteins, ectodomains, and/or fusion proteins, can be formulated to ensure proper distribution in vivo. For example, the blood-brain barrier (BBB) excludes many highly hydrophilic compounds. To ensure that the therapeutic compounds according to at least some embodiments of the invention cross the BBB (if desired), they can be formulated, for example, in liposomes. For methods of manufacturing liposomes, see, e.g., U.S. Pat. Nos. 4,522,811; 5,374,548; and 5,399,331. The liposomes may comprise one or more moieties which are selectively transported into specific cells or organs, thus enhance targeted drug delivery (see, e.g., V. V. Ranade (1989) *J. Clin. Pharmacol.* 29:685). Exemplary targeting moieties include folate or biotin (see, e.g., U.S. Pat. No. 5,416,016 to Low et al.); mannosides (Umezawa et al., (1988) *Biochem. Biophys. Res. Commun.* 153:1038); antibodies (P. G. Bloeman et al. (1995) *FEBS Lett.* 357:140; M. Owais et al. (1995) *Antimicrob. Agents Chemother.* 39:180); surfactant protein A receptor (Briscoe et al. (1995) *Am. J. Physiol.* 1233:134); p120 (Schreier et al. (1994) *J. Biol. Chem.* 269:9090); see also K. Keinanen; M. L. Laukkanen (1994) *FEBS Lett.* 346:123; J. J. Killian; I. J. Fidler (1994) *Immunomethods* 4:273.

The anti-LY6G6F, anti-VSIG10, anti-TMEM25 and anti-LSR antibodies, according to at least some embodiments of the present invention, can be used as neutralizing antibodies. A Neutralizing antibody (Nabs), is an antibody that is capable of binding and neutralizing or inhibiting a specific antigen thereby inhibiting its biological effect, for example by blocking the receptors on the cell or the virus, inhibiting the binding of the virus to the host cell. NAbs will partially or completely abrogate the biological action of an agent by either blocking an important surface molecule needed for its activity or by interfering with the binding of the agent to its receptor on a target cell.

In yet another embodiment, immunoconjugates of the invention can be used to target compounds (e.g., therapeutic agents, labels, cytotoxins, radiotoxins immunosuppressants, etc.) to cells which have LY6G6F, VSIG10, TMEM25 and/or LSR cell surface receptors by linking such compounds to the antibody. Thus, the invention also provides methods for localizing ex vivo or in vivo cells expressing LY6G6F, VSIG10, TMEM25 and/or LSR (e.g., with a detectable label, such as a

radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor). Alternatively, the immunoconjugates can be used to kill cells which have LY6G6F, VSIG10, TMEM25 and/or LSR cell surface receptors by targeting cytotoxins or radiotoxins to LY6G6F, VSIG10, TMEM25 and/or LSR antigen.

Diagnostic Uses of LY6G6F, VSIG10, TMEM25 and/or LSR Polypeptides and Corresponding Polynucleotides

According to some embodiments, the sample taken from a subject (patient) to perform the diagnostic assay according to at least some embodiments of the present invention is selected from the group consisting of a body fluid or secretion including but not limited to blood, serum, urine, plasma, prostatic fluid, seminal fluid, semen, the external secretions of the skin, respiratory, intestinal, and genitourinary tracts, tears, cerebrospinal fluid, synovial fluid, sputum, saliva, milk, peritoneal fluid, pleural fluid, cyst fluid, secretions of the breast ductal system (and/or lavage thereof), broncho alveolar lavage, lavage of the reproductive system and lavage of any other part of the body or system in the body; samples of any organ including isolated cells or tissues, wherein the cell or tissue can be obtained from an organ selected from, but not limited to lung, colon, ovarian and/or breast tissue; stool or a tissue sample, or any combination thereof. In some embodiments, the term encompasses samples of in vivo cell culture constituents. Prior to be subjected to the diagnostic assay, the sample can optionally be diluted with a suitable eluant.

In some embodiments, the phrase "marker" in the context of the present invention refers to a nucleic acid fragment, a peptide, or a polypeptide, which is differentially present in a sample taken from patients (subjects) having one of the herein-described diseases or conditions, as compared to a comparable sample taken from subjects who do not have one of the above-described diseases or conditions.

In some embodiments, the phrase "differentially present" refers to differences in the quantity or quality of a marker present in a sample taken from patients having one of the herein-described diseases or conditions as compared to a comparable sample taken from patients who do not have one of the herein-described diseases or conditions. For example, a nucleic acid fragment may optionally be differentially present between the two samples if the amount of the nucleic acid fragment in one sample is significantly different from the amount of the nucleic acid fragment in the other sample, for example as measured by hybridization and/or NAT-based assays. A polypeptide is differentially present between the two samples if the amount of the polypeptide in one sample is significantly different from the amount of the polypeptide in the other sample. It should be noted that if the marker is detectable in one sample and not detectable in the other, then such a marker can be considered to be differentially present. Optionally, a relatively low amount of up-regulation may serve as the marker, as described herein. One of ordinary skill in the art could easily determine such relative levels of the markers; further guidance is provided in the description of each individual marker below.

In some embodiments, the phrase "diagnostic" means identifying the presence or nature of a pathologic condition. Diagnostic methods differ in their sensitivity and specificity. The "sensitivity" of a diagnostic assay is the percentage of diseased individuals who test positive (percent of "true positives"). Diseased individuals not detected by the assay are "false negatives." Subjects who are not diseased and who test negative in the assay are termed "true negatives." The "specificity" of a diagnostic assay is 1 minus the false positive rate, where the "false positive" rate is defined as the proportion of those without the disease who test positive. While a particular

diagnostic method may not provide a definitive diagnosis of a condition, it suffices if the method provides a positive indication that aids in diagnosis.

As used herein the term “diagnosis” refers to the process of identifying a medical condition or disease by its signs, symptoms, and in particular from the results of various diagnostic procedures, including e.g. detecting the expression of the nucleic acids or polypeptides according to at least some embodiments of the invention in a biological sample (e.g. in cells, tissue or serum, as defined below) obtained from an individual. Furthermore, as used herein the term “diagnosis” encompasses screening for a disease, detecting a presence or a severity of a disease, providing prognosis of a disease, monitoring disease progression or relapse, as well as assessment of treatment efficacy and/or relapse of a disease, disorder or condition, as well as selecting a therapy and/or a treatment for a disease, optimization of a given therapy for a disease, monitoring the treatment of a disease, and/or predicting the suitability of a therapy for specific patients or subpopulations or determining the appropriate dosing of a therapeutic product in patients or subpopulations. The diagnostic procedure can be performed in vivo or in vitro.

In some embodiments, the phrase “qualitative” when in reference to differences in expression levels of a polynucleotide or polypeptide as described herein, refers to the presence versus absence of expression, or in some embodiments, the temporal regulation of expression, or in some embodiments, the timing of expression, or in some embodiments, any post-translational modifications to the expressed molecule, and others, as will be appreciated by one skilled in the art. In some embodiments, the phrase “quantitative” when in reference to differences in expression levels of a polynucleotide or polypeptide as described herein, refers to absolute differences in quantity of expression, as determined by any means, known in the art, or in other embodiments, relative differences, which may be statistically significant, or in some embodiments, when viewed as a whole or over a prolonged period of time, etc., indicate a trend in terms of differences in expression.

In some embodiments, the term “diagnosing” refers to classifying a disease or a symptom, determining a severity of the disease, monitoring disease progression, forecasting an outcome of a disease and/or prospects of recovery. The term “detecting” may also optionally encompass any of the above.

Diagnosis of a disease according to the present invention can, in some embodiments, be affected by determining a level of a polynucleotide or a polypeptide of the present invention in a biological sample obtained from the subject, wherein the level determined can be correlated with predisposition to, or presence or absence of the disease. It should be noted that a “biological sample obtained from the subject” may also optionally comprise a sample that has not been physically removed from the subject, as described in greater detail below.

In some embodiments, the term “level” refers to expression levels of RNA and/or protein or to DNA copy number of a marker of the present invention.

Typically the level of the marker in a biological sample obtained from the subject is different (i.e., increased or decreased) from the level of the same marker in a similar sample obtained from a healthy individual (examples of biological samples are described herein).

Numerous well known tissue or fluid collection methods can be utilized to collect the biological sample from the subject in order to determine the level of DNA, RNA and/or polypeptide of the marker of interest in the subject.

Examples include, but are not limited to, fine needle biopsy, needle biopsy, core needle biopsy and surgical biopsy (e.g., brain biopsy), and lavage. Regardless of the procedure employed, once a biopsy/sample is obtained the level of the marker can be determined and a diagnosis can thus be made.

Determining the level of the same marker in normal tissues of the same origin is preferably effected along-side to detect an elevated expression and/or amplification and/or a decreased expression, of the marker as opposed to the normal tissues.

In some embodiments, the term “test amount” of a marker refers to an amount of a marker in a subject’s sample that is consistent with a diagnosis of a particular disease or condition. A test amount can be either in absolute amount (e.g., microgram/ml) or a relative amount (e.g., relative intensity of signals).

In some embodiments, the term “control amount” of a marker can be any amount or a range of amounts to be compared against a test amount of a marker. For example, a control amount of a marker can be the amount of a marker in a patient with a particular disease or condition or a person without such a disease or condition. A control amount can be either in absolute amount (e.g., microgram/ml) or a relative amount (e.g., relative intensity of signals).

In some embodiments, the term “detect” refers to identifying the presence, absence or amount of the object to be detected.

In some embodiments, the term “label” includes any moiety or item detectable by spectroscopic, photo chemical, biochemical, immunochemical, or chemical means. For example, useful labels include ³²P, ³⁵S, fluorescent dyes, electron-dense reagents, enzymes (e.g., as commonly used in an ELISA), biotin-streptavidin, dioxigenin, haptens and proteins for which antisera or monoclonal antibodies are available, or nucleic acid molecules with a sequence complementary to a target. The label often generates a measurable signal, such as a radioactive, chromogenic, or fluorescent signal, that can be used to quantify the amount of bound label in a sample. The label can be incorporated in or attached to a primer or probe either covalently, or through ionic, van der Waals or hydrogen bonds, e.g., incorporation of radioactive nucleotides, or biotinylated nucleotides that are recognized by streptavidin. The label may be directly or indirectly detectable. Indirect detection can involve the binding of a second label to the first label, directly or indirectly. For example, the label can be the ligand of a binding partner, such as biotin, which is a binding partner for streptavidin, or a nucleotide sequence, which is the binding partner for a complementary sequence, to which it can specifically hybridize. The binding partner may itself be directly detectable, for example, an antibody may be itself labeled with a fluorescent molecule. The binding partner also may be indirectly detectable, for example, a nucleic acid having a complementary nucleotide sequence can be a part of a branched DNA molecule that is in turn detectable through hybridization with other labeled nucleic acid molecules (see, e.g., P. D. Fahrlander and A. Klausner, *Bio/Technology* 6:1165 (1988)). Quantitation of the signal is achieved by, e.g., scintillation counting, densitometry, or flow cytometry.

Exemplary detectable labels, optionally and preferably for use with immunoassays, include but are not limited to magnetic beads, fluorescent dyes, radiolabels, enzymes (e.g., horse radish peroxidase, alkaline phosphatase and others commonly used in an ELISA), and calorimetric labels such as colloidal gold or colored glass or plastic beads. Alternatively, the marker in the sample can be detected using an indirect assay, wherein, for example, a second, labeled antibody is

used to detect bound marker-specific antibody, and/or in a competition or inhibition assay wherein, for example, a monoclonal antibody which binds to a distinct epitope of the marker are incubated simultaneously with the mixture.

"Immunoassay" is an assay that uses an antibody to specifically bind an antigen. The immunoassay is characterized by the use of specific binding properties of a particular antibody to isolate, target, and/or quantify the antigen.

The phrase "specifically (or selectively) binds" to an antibody or "specifically (or selectively) immunoreactive with," or "specifically interacts or binds" when referring to a protein or peptide (or other epitope), refers, in some embodiments, to a binding reaction that is determinative of the presence of the protein in a heterogeneous population of proteins and other biologics. Thus, under designated immunoassay conditions, the specified antibodies bind to a particular protein at least two times greater than the background (non-specific signal) and do not substantially bind in a significant amount to other proteins present in the sample. Specific binding to an antibody under such conditions may require an antibody that is selected for its specificity for a particular protein. For example, polyclonal antibodies raised to seminal basic protein from specific species such as rat, mouse, or human can be selected to obtain only those polyclonal antibodies that are specifically immunoreactive with seminal basic protein and not with other proteins, except for polymorphic variants and alleles of seminal basic protein. This selection may be achieved by subtracting out antibodies that cross-react with seminal basic protein molecules from other species. A variety of immunoassay formats may be used to select antibodies specifically immunoreactive with a particular protein. For example, solid-phase ELISA immunoassays are routinely used to select antibodies specifically immunoreactive with a protein (see, e.g., Harlow & Lane, *Antibodies, A Laboratory Manual* (1988), for a description of immunoassay formats and conditions that can be used to determine specific immunoreactivity). Typically a specific or selective reaction will be at least twice background signal or noise and more typically more than 10 to 100 times background.

In another embodiment, this invention provides a method for detecting the polypeptides of this invention in a biological sample, comprising: contacting a biological sample with an antibody specifically recognizing a polypeptide according to the present invention and detecting said interaction; wherein the presence of an interaction correlates with the presence of a polypeptide in the biological sample.

In some embodiments of the present invention, the polypeptides described herein are non-limiting examples of markers for diagnosing a disease and/or an indicative condition. Each marker of the present invention can be used alone or in combination, for various uses, including but not limited to, prognosis, prediction, screening, early diagnosis, determination of progression, therapy selection and treatment monitoring of a disease and/or an indicative condition.

In a related object the detected diseases will include cancers such as non-solid and solid tumors, sarcomas and hematological malignancies.

In another related object the detected diseases will include autoimmune disorders, rejection of any organ transplant and/or Graft versus host disease.

Each polypeptide/polynucleotide of the present invention can be used alone or in combination, for various uses, including but not limited to, prognosis, prediction, screening, early diagnosis, determination of progression, therapy selection and treatment monitoring of disease and/or an indicative condition, as detailed above.

Such a combination may optionally comprise any subcombination of markers, and/or a combination featuring at least one other marker, for example a known marker. Furthermore, such a combination may optionally and preferably be used as described above with regard to determining a ratio between a quantitative or semi-quantitative measurement of any marker described herein to any other marker described herein, and/or any other known marker, and/or any other marker.

In some embodiments of the present invention, there are provided of methods, uses, devices and assays for the diagnosis of a disease or condition. Optionally a plurality of markers may be used with the present invention. The plurality of markers may optionally include a markers described herein, and/or one or more known markers. The plurality of markers is preferably then correlated with the disease or condition. For example, such correlating may optionally comprise determining the concentration of each of the plurality of markers, and individually comparing each marker concentration to a threshold level. Optionally, if the marker concentration is above or below the threshold level (depending upon the marker and/or the diagnostic test being performed), the marker concentration correlates with the disease or condition. Optionally and preferably, a plurality of marker concentrations correlates with the disease or condition.

Alternatively, such correlating may optionally comprise determining the concentration of each of the plurality of markers, calculating a single index value based on the concentration of each of the plurality of markers, and comparing the index value to a threshold level.

Also alternatively, such correlating may optionally comprise determining a temporal change in at least one of the markers, and wherein the temporal change is used in the correlating step.

Also alternatively, such correlating may optionally comprise determining whether at least "X" number of the plurality of markers has a concentration outside of a predetermined range and/or above or below a threshold (as described above). The value of "X" may optionally be one marker, a plurality of markers or all of the markers; alternatively or additionally, rather than including any marker in the count for "X", one or more specific markers of the plurality of markers may optionally be required to correlate with the disease or condition (according to a range and/or threshold).

Also alternatively, such correlating may optionally comprise determining whether a ratio of marker concentrations for two markers is outside a range and/or above or below a threshold. Optionally, if the ratio is above or below the threshold level and/or outside a range, the ratio correlates with the disease or condition.

Optionally, a combination of two or more these correlations may be used with a single panel and/or for correlating between a plurality of panels.

Optionally, the method distinguishes a disease or condition with a sensitivity of at least 70% at a specificity of at least 85% when compared to normal subjects. As used herein, sensitivity relates to the number of positive (diseased) samples detected out of the total number of positive samples present; specificity relates to the number of true negative (non-diseased) samples detected out of the total number of negative samples present. Preferably, the method distinguishes a disease or condition with a sensitivity of at least 80% at a specificity of at least 90% when compared to normal subjects. More preferably, the method distinguishes a disease or condition with a sensitivity of at least 90% at a specificity of at least 90% when compared to normal subjects. Also more preferably, the method distinguishes a disease or condition with a sensitivity of at least 70% at a specificity of at least 85%

when compared to subjects exhibiting symptoms that mimic disease or condition symptoms.

A marker panel may be analyzed in a number of fashions well known to those of skill in the art. For example, each member of a panel may be compared to a "normal" value, or a value indicating a particular outcome. A particular diagnosis/prognosis may depend upon the comparison of each marker to this value; alternatively, if only a subset of markers is outside of a normal range, this subset may be indicative of a particular diagnosis/prognosis. The skilled artisan will also understand that diagnostic markers, differential diagnostic markers, prognostic markers, time of onset markers, disease or condition differentiating markers, etc., may be combined in a single assay or device. Markers may also be commonly used for multiple purposes by, for example, applying a different threshold or a different weighting factor to the marker for the different purposes.

In one embodiment, the panels comprise markers for the following purposes: diagnosis of a disease; diagnosis of disease and indication if the disease is in an acute phase and/or if an acute attack of the disease has occurred; diagnosis of disease and indication if the disease is in a non-acute phase and/or if a non-acute attack of the disease has occurred; indication whether a combination of acute and non-acute phases or attacks has occurred; diagnosis of a disease and prognosis of a subsequent adverse outcome; diagnosis of a disease and prognosis of a subsequent acute or non-acute phase or attack; disease progression (for example for cancer, such progression may include for example occurrence or recurrence of metastasis).

The above diagnoses may also optionally include differential diagnosis of the disease to distinguish it from other diseases, including those diseases that may feature one or more similar or identical symptoms.

In certain embodiments, one or more diagnostic or prognostic indicators are correlated to a condition or disease by merely the presence or absence of the indicators. In other embodiments, threshold levels of a diagnostic or prognostic indicators can be established, and the level of the indicators in a patient sample can simply be compared to the threshold levels. The sensitivity and specificity of a diagnostic and/or prognostic test depends on more than just the analytical "quality" of the test—they also depend on the definition of what constitutes an abnormal result. In practice, Receiver Operating Characteristic curves, or "ROC" curves, are typically calculated by plotting the value of a variable versus its relative frequency in "normal" and "disease" populations, and/or by comparison of results from a subject before, during and/or after treatment.

According to at least some embodiments of the present invention, LY6G6F, VSIG10, TMEM25 and/or LSR protein, polynucleotide or a fragment thereof, may be featured as a biomarker for detecting disease and/or an indicative condition, as detailed above.

According to still other embodiments, the present invention optionally and preferably encompasses any amino acid sequence or fragment thereof encoded by a nucleic acid sequence corresponding to LY6G6F, VSIG10, TMEM25 and/or LSR as described herein. Any oligopeptide or peptide relating to such an amino acid sequence or fragment thereof may optionally also (additionally or alternatively) be used as a biomarker.

In still other embodiments, the present invention provides a method for detecting a polynucleotide of this invention in a biological sample, using NAT based assays, comprising: hybridizing the isolated nucleic acid molecules or oligonucleotide fragments of at least about a minimum length to a

nucleic acid material of a biological sample and detecting a hybridization complex; wherein the presence of a hybridization complex correlates with the presence of the polynucleotide in the biological sample. Non-limiting examples of methods or assays are described below.

The present invention also relates to kits based upon such diagnostic methods or assays. Also within the scope of the present invention are kits comprising the LY6G6F, VSIG10, TMEM25 and/or LSR protein or LY6G6F, VSIG10, TMEM25 and/or LSR conjugates or antibody compositions of the invention (e.g., human antibodies, bispecific or multi-specific molecules, or immunoconjugates) and instructions for use. The kit can further contain one or more additional reagents, such as an immunosuppressive reagent, a cytotoxic agent or a radiotoxic agent, or one or more additional human antibodies according to at least some embodiments of the invention (e.g., a human antibody having a complementary activity which binds to an epitope in the antigen distinct from the first human antibody).

Nucleic Acid Technology (NAT) Based Assays:

Detection of a nucleic acid of interest in a biological sample may also optionally be effected by NAT-based assays, which involve nucleic acid amplification technology, such as PCR for example (or variations thereof such as real-time PCR for example). As used herein, a "primer" defines an oligonucleotide which is capable of annealing to (hybridizing with) a target sequence, thereby creating a double stranded region which can serve as an initiation point for DNA synthesis under suitable conditions. Amplification of a selected, or target, nucleic acid sequence may be carried out by a number of suitable methods known in the art. Non-limiting examples of amplification techniques include polymerase chain reaction (PCR), ligase chain reaction (LCR), strand displacement amplification (SDA), transcription-based amplification, the q3 replicase system and NASBA (Kwoh et al., 1989, Proc. Natl. Acad. Sci. USA 86, 1173-1177; Lizardi et al., 1988, BioTechnology 6:1197-1202; Malek et al., 1994, Methods Mol. Biol., 28:253-260; and Sambrook et al., 1989, supra). Non-limiting examples of Nucleic Acid Technology-based assay is selected from the group consisting of a PCR, Real-Time PCR, LCR, Self-Sustained Synthetic Reaction, Q-Beta Replicase, Cycling probe reaction, Branched DNA, RFLP analysis, DGGE/TGGE, Single-Strand Conformation Polymorphism, Dideoxy fingerprinting, microarrays, Fluorescence In Situ Hybridization and Comparative Genomic Hybridization. The terminology "amplification pair" (or "primer pair") refers herein to a pair of oligonucleotides (oligos) of the present invention, which are selected to be used together in amplifying a selected nucleic acid sequence by one of a number of types of amplification processes, preferably a polymerase chain reaction. As commonly known in the art, the oligos are designed to bind to a complementary sequence under selected conditions. In one particular embodiment, amplification of a nucleic acid sample from a patient is amplified under conditions which favor the amplification of the most abundant differentially expressed nucleic acid. In one preferred embodiment, RT-PCR is carried out on an mRNA sample from a patient under conditions which favor the amplification of the most abundant mRNA. In another preferred embodiment, the amplification of the differentially expressed nucleic acids is carried out simultaneously. It will be realized by a person skilled in the art that such methods could be adapted for the detection of differentially expressed proteins instead of differentially expressed nucleic acid sequences. The nucleic acid (i.e. DNA or RNA) for practicing the present invention may be obtained according to well known methods.

Oligonucleotide primers of the present invention may be of any suitable length, depending on the particular assay format and the particular needs and targeted genomes employed. Optionally, the oligonucleotide primers are at least 12 nucleotides in length, preferably between 15 and 24 molecules, and they may be adapted to be especially suited to a chosen nucleic acid amplification system. As commonly known in the art, the oligonucleotide primers can be designed by taking into consideration the melting point of hybridization thereof with its targeted sequence (Sambrook et al., 1989, *Molecular Cloning-A Laboratory Manual*, 2nd Edition, CSH Laboratories; Ausubel et al., 1989, in *Current Protocols in Molecular Biology*, John Wiley & Sons Inc., N.Y.).

Immunoassays

In another embodiment of the present invention, an immunoassay can be used to qualitatively or quantitatively detect and analyze markers in a sample. This method comprises: providing an antibody that specifically binds to a marker; contacting a sample with the antibody; and detecting the presence of a complex of the antibody bound to the marker in the sample.

To prepare an antibody that specifically binds to a marker, purified protein markers can be used. Antibodies that specifically bind to a protein marker can be prepared using any suitable methods known in the art.

After the antibody is provided, a marker can be detected and/or quantified using any of a number of well recognized immunological binding assays. Useful assays include, for example, an enzyme immune assay (EIA) such as enzyme-linked immunosorbent assay (ELISA), a radioimmune assay (RIA), a Western blot assay, or a slot blot assay see, e.g., U.S. Pat. Nos. 4,366,241; 4,376,110; 4,517,288; and 4,837,168). Generally, a sample obtained from a subject can be contacted with the antibody that specifically binds the marker.

Optionally, the antibody can be fixed to a solid support to facilitate washing and subsequent isolation of the complex, prior to contacting the antibody with a sample. Examples of solid supports include but are not limited to glass or plastic in the form of, e.g., a microtiter plate, a stick, a bead, or a microbead. Antibodies can also be attached to a solid support.

After incubating the sample with antibodies, the mixture is washed and the antibody-marker complex formed can be detected. This can be accomplished by incubating the washed mixture with a detection reagent. Alternatively, the marker in the sample can be detected using an indirect assay, wherein, for example, a second, labeled antibody is used to detect bound marker-specific antibody, and/or in a competition or inhibition assay wherein, for example, a monoclonal antibody which binds to a distinct epitope of the marker are incubated simultaneously with the mixture.

Throughout the assays, incubation and/or washing steps may be required after each combination of reagents. Incubation steps can vary from about 5 seconds to several hours, preferably from about 5 minutes to about 24 hours. However, the incubation time will depend upon the assay format, marker, volume of solution, concentrations and the like. Usually the assays will be carried out at ambient temperature, although they can be conducted over a range of temperatures, such as 10° C. to 40° C.

The immunoassay can be used to determine a test amount of a marker in a sample from a subject. First, a test amount of a marker in a sample can be detected using the immunoassay methods described above. If a marker is present in the sample, it will form an antibody-marker complex with an antibody that specifically binds the marker under suitable incubation conditions described above. The amount of an antibody-marker complex can optionally be determined by comparing

to a standard. As noted above, the test amount of marker need not be measured in absolute units, as long as the unit of measurement can be compared to a control amount and/or signal.

Radio-immunoassay (RIA): In one version, this method involves precipitation of the desired substrate and in the methods detailed herein below, with a specific antibody and radio-labeled antibody binding protein (e.g., protein A labeled with ¹²⁵I) immobilized on a precipitable carrier such as agarose beads. The number of counts in the precipitated pellet is proportional to the amount of substrate.

In an alternate version of the RIA, a labeled substrate and an unlabelled antibody binding protein are employed. A sample containing an unknown amount of substrate is added in varying amounts. The decrease in precipitated counts from the labeled substrate is proportional to the amount of substrate in the added sample.

Enzyme linked immunosorbent assay (ELISA): This method involves fixation of a sample (e.g., fixed cells or a proteinaceous solution) containing a protein substrate to a surface such as a well of a microtiter plate. A substrate specific antibody coupled to an enzyme is applied and allowed to bind to the substrate. Presence of the antibody is then detected and quantitated by a colorimetric reaction employing the enzyme coupled to the antibody. Enzymes commonly employed in this method include horseradish peroxidase and alkaline phosphatase. If well calibrated and within the linear range of response, the amount of substrate present in the sample is proportional to the amount of color produced. A substrate standard is generally employed to improve quantitative accuracy.

Western blot: This method involves separation of a substrate from other protein by means of an acrylamide gel followed by transfer of the substrate to a membrane (e.g., nylon or PVDF). Presence of the substrate is then detected by antibodies specific to the substrate, which are in turn detected by antibody binding reagents. Antibody binding reagents may be, for example, protein A, or other antibodies. Antibody binding reagents may be radiolabeled or enzyme linked as described hereinabove. Detection may be by autoradiography, colorimetric reaction or chemiluminescence. This method allows both quantitation of an amount of substrate and determination of its identity by a relative position on the membrane which is indicative of a migration distance in the acrylamide gel during electrophoresis.

Immunohistochemical analysis: This method involves detection of a substrate in situ in fixed cells by substrate specific antibodies. The substrate specific antibodies may be enzyme linked or linked to fluorophores. Detection is by microscopy and subjective evaluation. If enzyme linked antibodies are employed, a colorimetric reaction may be required.

Fluorescence activated cell sorting (FACS): This method involves detection of a substrate in situ in cells by substrate specific antibodies. The substrate specific antibodies are linked to fluorophores. Detection is by means of a cell sorting machine which reads the wavelength of light emitted from each cell as it passes through a light beam. This method may employ two or more antibodies simultaneously.

Radio-Imaging Methods

These methods include but are not limited to, positron emission tomography (PET) single photon emission computed tomography (SPECT). Both of these techniques are non-invasive, and can be used to detect and/or measure a wide variety of tissue events and/or functions, such as detecting cancerous cells for example. Unlike PET, SPECT can optionally be used with two labels simultaneously. SPECT has some

other advantages as well, for example with regard to cost and the types of labels that can be used. For example, U.S. Pat. No. 6,696,686 describes the use of SPECT for detection of breast cancer, and is hereby incorporated by reference as if fully set forth herein.

Theranostics:

The term theranostics describes the use of diagnostic testing to diagnose the disease, choose the correct treatment regime according to the results of diagnostic testing and/or monitor the patient response to therapy according to the results of diagnostic testing. Theranostic tests can be used to select patients for treatments that are particularly likely to benefit them and unlikely to produce side-effects. They can also provide an early and objective indication of treatment efficacy in individual patients, so that (if necessary) the treatment can be altered with a minimum of delay. For example: DAKO and Genentech together created HercepTest and Herceptin (trastuzumab) for the treatment of breast cancer, the first theranostic test approved simultaneously with a new therapeutic drug. In addition to HercepTest (which is an immunohistochemical test), other theranostic tests are in development which use traditional clinical chemistry, immunoassay, cell-based technologies and nucleic acid tests. PPGx's recently launched TPMT (thiopurine S-methyltransferase) test, which is enabling doctors to identify patients at risk for potentially fatal adverse reactions to 6-mercaptopurine, an agent used in the treatment of leukemia. Also, Nova Molecular pioneered SNP genotyping of the apolipoprotein E gene to predict Alzheimer's disease patients' responses to cholinomimetic therapies and it is now widely used in clinical trials of new drugs for this indication. Thus, the field of theranostics represents the intersection of diagnostic testing information that predicts the response of a patient to a treatment with the selection of the appropriate treatment for that particular patient.

Surrogate Markers:

A surrogate marker is a marker, that is detectable in a laboratory and/or according to a physical sign or symptom on the patient, and that is used in therapeutic trials as a substitute for a clinically meaningful endpoint. The surrogate marker is a direct measure of how a patient feels, functions, or survives which is expected to predict the effect of the therapy. The need for surrogate markers mainly arises when such markers can be measured earlier, more conveniently, or more frequently than the endpoints of interest in terms of the effect of a treatment on a patient, which are referred to as the clinical endpoints. Ideally, a surrogate marker should be biologically plausible, predictive of disease progression and measurable by standardized assays (including but not limited to traditional clinical chemistry, immunoassay, cell-based technologies, nucleic acid tests and imaging modalities).

The therapeutic compositions (e.g., human antibodies, multispecific and bispecific molecules and immunoconjugates) according to at least some embodiments of the invention which have complement binding sites, such as portions from IgG1, -2, or -3 or IgM which bind complement, can also be used in the presence of complement. In one embodiment, ex vivo treatment of a population of cells comprising target cells with a binding agent according to at least some embodiments of the invention and appropriate effector cells can be supplemented by the addition of complement or serum containing complement. Phagocytosis of target cells coated with a binding agent according to at least some embodiments of the invention can be improved by binding of complement proteins. In another embodiment target cells coated with the compositions (e.g., human antibodies, multispecific and bispecific molecules) according to at least some embodi-

ments of the invention can also be lysed by complement. In yet another embodiment, the compositions according to at least some embodiments of the invention do not activate complement.

The therapeutic compositions (e.g., human antibodies, multispecific and bispecific molecules and immunoconjugates) according to at least some embodiments of the invention can also be administered together with complement. Thus, according to at least some embodiments of the invention there are compositions, comprising human antibodies, multispecific or bispecific molecules and serum or complement. These compositions are advantageous in that the complement is located in close proximity to the human antibodies, multispecific or bispecific molecules. Alternatively, the human antibodies, multispecific or bispecific molecules according to at least some embodiments of the invention and the complement or serum can be administered separately.

The present invention is further illustrated by the following examples. This information and examples is illustrative and should not be construed as further limiting. The contents of all figures and all references, patents and published patent applications cited throughout this application are expressly incorporated herein by reference.

EXAMPLES

Example 1

Expression Pattern of the Proteins According to at Least Some Embodiments of The Invention Using MED Discovery Engine

MED is a proprietary software platform for collection of public gene-expression data, normalization, annotation and performance of various queries. Expression data from the most widely used Affymetrix microarrays is downloaded from the Gene Expression Omnibus (GEO—www.ncbi.nlm.nih.gov/GEO). Data is multiplicatively normalized by setting the 95 percentile to a constant value (normalized expression=1200), and noise is filtered by setting the lower 30% to 0. Experiments are annotated, first automatically, and then manually, to identify tissue and condition, and chips are grouped according to this annotation, and cross verification of this grouping by comparing the overall expression pattern of the genes of each chip to the overall average expression pattern of the genes in this group. Each probeset in each group is assigned an expression value which is the median of the expressions of that probeset in all chips included in the group. The vector of expression of all probesets within a certain group forms the virtual chip of that group, and the collection of all such virtual chips is a virtual panel. The panel (or sub-panels) can be queried to identify probesets with a required behavior (e.g. specific expression in a sub-set of tissues, or differential expression between disease and healthy tissues). These probesets are linked to LEADS contigs and to RefSeqs (<http://www.ncbi.nlm.nih.gov/RefSeq/>) by probe-level mapping, for further analysis.

The Affymetrix platforms that are downloaded are HG-U95A and the HG-U133 family (A,B, A2.0 and PLUS 2.0). Three virtual panels were created: U95 and U133 Plus 2.0, based on the corresponding Affymetrix platforms, and U133 which uses the set of common probesets for HG-U133A, HG-U133A2.0 and HG-U133 PLUS 2.0+.

The results of the MED discovery engine are presented in scatter plots. The scatter plot is a compact representation of a given panel (collection of groups). The y-axis is the (normalized) expression and the x-axis describes the groups in the

panel. For each group, the median expression is represented by a solid marker, and the expression values of the different chips in the group are represented by small dashes ("-"). The groups are ordered and marked as follows—"Other" groups (e.g. benign, non-cancer diseases, etc.) with a triangle, Treated cells with a square, Normal with a circle, Matched with a cross, and

Cancer with a diamond. The number of chips in each group is also written adjacent to its name.

The MED discovery engine was used to assess the expression of VSIG10 transcripts. Expression data for Affymetrix probe sets 220137_at representing the VSIG10 gene data is shown in FIG. 3 (for all figures related to the MED discovery engine, a division was made into "A", "B", etc for reasons of space only, so as to be able to show all probe results). As evident from the scatter plot, presented in FIG. 3, the expression of VSIG10 transcripts detectable with the above probe sets was observed in several groups of cells from the immune system, mainly in leukocytes. In various cancer conditions, differential expression was observed, for example on CD10+ leukocytes from ALL (Acute Lymphoblastic Leukemia) and BM-CD34+ cells from AML (Acute Myeloid Leukemia) cells.

FIG. 3 shows a scatter plot, demonstrating the expression of VSIG10 transcripts that encode the VSIG10 proteins, on a virtual panel of all tissues and conditions using MED discovery engine.

MED discovery engine was used to assess the expression of LSR transcripts. Expression data for Affymetrix probe sets 208190_s_at representing the LSR gene data is shown in FIG. 4. As evident from the scatter plot, presented in FIG. 4, the expression of LSR transcripts detectable with the above probe sets was observed in several groups of cells from the immune system, mainly in bone marrow cells. High expression of LSR transcripts was also observed in various cancerous conditions of tissues, such as in breast, lung, ovary, pancreas, prostate and skin cancers.

FIG. 4 shows a scatter plot, demonstrating the expression of LSR transcripts that encode the LSR proteins, on a virtual panel of all tissues and conditions using MED discovery engine.

Example 2

Methods Used to Analyze the Expression of the RNA Encoding LY6G6F, VSIG10, TMEM25 and/or LSR Proteins

The targets according to at least some embodiments of the present invention were tested with regard to their expression in various cancerous and non-cancerous tissue samples. A description of the samples used in the Ovary cancer testing panel is provided in Table 1 below. A description of the samples used in the Breast cancer testing panel is provided in Table 2 below. A description of the samples used in the Lung cancer testing panel is provided in Table 3. A description of the samples used in the Healthy testing panel is provided in Table 4. A description of the samples used in the Kidney cancer testing panel is provided in Table 5. A description of the samples used in the Liver cancer testing panel is provided in Table 6. Tests were then performed as described in the Materials and Methods section below.

Materials and Methods

RNA Preparation—

RNA was obtained from ABS (Wilmington, Del. 19801, USA, <http://www.absbioreagents.com>), BioChain Inst. Inc. (Hayward, Calif. 94545 USA, www.biochain.com), GOG for

ovary samples—Pediatric Cooperative Human Tissue Network, Gynecologic Oncology Group Tissue Bank, Children Hospital of Columbus (Columbus Ohio 43205 USA), Ambion (Austin, Tex. 78744 USA, <http://www.ambion.com>), Analytical Biological Services Inc. (Wilmington, Del. 19801 USA, www.absbioreagents.com), Asternad (Detroit, Mich. 48202-3420, USA, www.asterand.com), Genomics Collaborative Inc. a Division of Seracare (Cambridge, Mass. 02139, USA, www.genomicsinc.com), The Tel Aviv Sourasky Medical Center Ichilov Hospital (Tel-Aviv, ISRAEL, www.tasmc.org.il/e/) and from The Chaim Sheba Medical Center (Tel-Hashomer, ISRAEL, eng.sheba.co.il). RNA samples were obtained from patients or from postmortem. All total RNA samples were treated with DNaseI (Ambion).

RT-PCR for Ovary, Kidney and Healthy Panel—

10 ug of Purified RNA was mixed with Random Hexamer primers (Applied Biosystems, according to manufactures instructions), 4 mM dNTPs, 12.5 µl of 10× MultiScribe™ buffer (Applied Biosystems), 6 (50 U/µL) RNasin (Promega) and 6 µl (50 U/µL) of MultiScribe (Applied Biosystems) in a total volume of 125 µl. The reaction was incubated for 10 min at 25° C., followed by further incubation at 37° C. for 2 hours. Then, the mixture was inactivated at 85° C. for 5 sec. The resulting cDNA was diluted 1:10-1:40 (depend on the panel calibration) in TE buffer (10 mM Tris pH=8, 1 mM EDTA pH=8).

Real-Time RT-PCR analysis was carried out as described below—cDNA (5 µl), prepared as described above, was used as a template for Real-Time PCR reactions (final volume of 20 µl) using the SYBR Green I assay (PE Applied Biosystem) with specific primers and UNG Enzyme (Eurogentech or ABI or Roche). The amplification was effected as follows: 50° C. for 2 min, 95° C. for 10 min, and then 40 cycles of 95° C. for 15 sec, followed by 60° C. for 30 sec, following by dissociation step. Detection was performed using the PE Applied Biosystem SDS 7000. The cycle in which the reactions achieved a threshold level of fluorescence (Ct=Threshold Cycle, described in detail below) was registered and was used to calculate the relative transcript quantity in the RT reactions. The relative quantity was calculated using the equation $Q = \text{efficiency}^{-Ct}$. The efficiency of the PCR reaction was calculated from a standard curve, created by using different dilutions of several reverse transcription (RT) reactions. To minimize inherent differences in the RT reaction, the resulting relative quantities were normalized using a normalization factor calculated in the following way:

The expression of several housekeeping (HSPK) genes was checked in every panel. The relative quantity (Q) of each housekeeping gene in each sample, calculated as described above, was divided by the median quantity of this gene in all panel samples to obtain the "Relative Q rel to MED". Then, for each sample the median of the "relative Q rel to MED" of the selected housekeeping genes was calculated and served as normalization factor of this sample for further calculations.

For each RT sample, the expression of the specific amplicon was normalized to the normalization factor calculated from the expression of different housekeeping genes. Housekeeping genes (HSPKG) used for Ovary, Kidney, Lung, Liver, Breast and Healthy panels are listed in Table 7.

The HSKGs that were used for Ovary and Healthy panels calibration are: HPRT1, SDHA and G6PD; The HSKP genes used for Kidney and Liver panel calibration are: G6PD, PBGD and SDHA; The HSKP genes used for Lung panel calibration are: UBC, PBGD, HPRT and SDHA; The HSKP genes used for Breast panel calibration are: G6PD, PBGD, RPL19 and SDHA;

TABLE 1

Ovary RNA details:				
sample name	Source	sample_id	DIAGNOSIS	CANCER_STAGE
1-As-SI-SER	Asterand	23074	SEROUS ADENOCARCINOMA	STAGE I
2-As-SI-SER	Asterand	22653	SEROUS ADENOCARCINOMA	STAGE I
3-As-SIB-SER	Asterand	18700	SEROUS ADENOCARCINOMA	STAGE IB
4-As-SIB-SER	Asterand	17646	SEROUS ADENOCARCINOMA	STAGE IB
5-As-SIC-SER	Asterand	15644	SEROUS ADENOCARCINOMA	STAGE IC
6-GC-SIIB-SER	GCI-1st_del	7B3DP	SEROUS ADENOCARCINOMA	STAGE IIB
7-As-SIIC-SER	Asterand	13268	SEROUS ADENOCARCINOMA	STAGE IIIC
8-GC-SIIC-SER	GCI-1st_del	3NTIS	SEROUS ADENOCARCINOMA	STAGE IIIC
9-GC-SIIC-SER	GCI-1st_del	CEJUS	SEROUS ADENOCARCINOMA	STAGE IIIC
10-GC-SIIC-SER	GCI-1st_del	1HI5H	SEROUS ADENOCARCINOMA	STAGE IIIC
11-GC-SIIC-SER	GCI-1st_del	7RMHZ	SEROUS ADENOCARCINOMA	STAGE IIIC
12-GC-SIIC-SER	GCI-1st_del	4WAAB	SEROUS ADENOCARCINOMA	STAGE IIIC
13-GC-SIIC-SER	GCI-1st_del	79Z67	SEROUS ADENOCARCINOMA	STAGE IIIC
14-GC-SIIC-SER	GCI-1st_del	DDSNL	SEROUS ADENOCARCINOMA	STAGE IIIC
15-GC-SIV-SER	GCI-1st_del	DH8PH	SEROUS ADENOCARCINOMA	STAGE IV
16-GC-SIA-ENDO	GCI-1st_del	E2WKF	ENDOMETROID ADENOCARCINOMA	STAGE IA
17-GC-SIA-ENDO	GCI-1st_del	HZ2EY	ENDOMETROID ADENOCARCINOMA	STAGE IA
18-GC-SIA-ENDO	GCI-1st_del	RWOIV	ENDOMETROID ADENOCARCINOMA	STAGE IA
19-GC-SIIA-ENDO	GCI-1st_del	1U52X	ENDOMETROID ADENOCARCINOMA	STAGE IIA
20-GC-SIIB-ENDO	GCI-1st_del	A17WS	ENDOMETROID ADENOCARCINOMA	STAGE IIB
21-GC-SIIC-ENDO	GCI-1st_del	1VT3I	ENDOMETROID ADENOCARCINOMA	STAGE IIIC
22-GC-SIIC-ENDO	GCI-1st_del	PZQXH	ENDOMETROID ADENOCARCINOMA	STAGE IIIC
23-GC-SIV-ENDO	GCI-1st_del	I8VHZ	ENDOMETROID ADENOCARCINOMA	STAGE IV
24-GC-SIC-MUC	GCI-1st_del	IMDA1	MUCINOUS ADENOCARCINOMA	STAGE IC
25-As-SIC-MUC	Asterand	12742	MUCINOUS ADENOCARCINOMA	STAGE IC
26-AB-SIC-MUC	ABS	A0139	Mucinous cystadenocarcinoma	Stage IC
27-AB-SIIIA-MUC	ABS	USA-00273	Papillary mucinous cystadenocarcinoma	STAGE IIIA
28-GC-SIIIA-MUC	GCI-2nd_del	RAFCW	MUCINOUS ADENOCARCINOMA	STAGE IIIA
29-As-SIIC-MUC	Asterand	23177	MUCINOUS ADENOCARCINOMA	STAGE IIIC
30-As-SIIC-MUC	Asterand	16103	MUCINOUS ADENOCARCINOMA	STAGE IIIC
31-GC-SIA-BRD	GCI-3rd_del	SC656	MUCINOUS BORDERLINE TUMOR	STAGE IA
32-GC-SIA-BRD	GCI-3rd_del	3D5FO	MUCINOUS BORDERLINE TUMOR	STAGE IA
33-GC-SIA-BRD	GCI-3rd_del	7JP3F	MUCINOUS BORDERLINE TUMOR	STAGE IA
34-GC-Muc-BNG	GCI-1st_del	QLIKY	BENIGN MUCINOUS CYSTADENOMA	
35-As-Muc-BNG	Asterand	16870	BENIGN MUCINOUS CYSTADENOMA	
36-GC-Muc-BNG	GCI-1st_del	943EC	BENIGN MUCINOUS CYSTADENOMA	
37-GC-Muc-BNG	GCI-2nd_del	JO8W7	BENIGN MUCINOUS CYSTADENOMA	
38-As-Ser-BNG	Asterand	17016	BENIGN SEROUS CYSTADENOMA	IA

TABLE 1-continued

Ovary RNA details:				
sample name	Source	sample_id	DIAGNOSIS	CANCER_STAGE
39-GO-Ser-BNG	GOG	99-06-G039	BENIGN SEROUS CYSTADENOMA	
40-GC-Ser-BNG	GCI-2nd_del	DQQ2F	BENIGN SEROUS CYSTADENOFIBROMA	
41-As-BM-N	Asterand	15690	NORMAL OVARY-BM	
42-As-BM-N	Asterand	16850	NORMAL OVARY-BM	
43-As-BM-N	Asterand	16848	NORMAL OVARY-BM	
44-GC-PS-N	GCI-4th_del	WPU1U	NORMAL OVARY-PS	
45-GC-PS-N	GCI-4th_del	Y9VHI	NORMAL OVARY-PS	
46-GC-PS-N	GCI-4th_del	76VM9	NORMAL OVARY-PS	
47-GC-PS-N	GCI-1st_del	DWHTZ	NORMAL OVARY-PS	
48-GC-PS-N	GCI-1st_del	SJ2R2	NORMAL OVARY-PS	
49-GC-PS-N	GCI-4th_del	9RQMN	NORMAL OVARY-PS	
50-GC-PS-N	GCI-1st_del	TOAE5	NORMAL OVARY-PS	
51-GC-PS-N	GCI-1st_del	TW9PM	NORMAL OVARY-PS	
52-GC-PS-N	GCI-4th_del	2VND2	NORMAL OVARY-PS	
53-GC-PS-N	GCI-1st_del	L629F	NORMAL OVARY-PS	
54-GC-PS-N	GCI-1st_del	XLB23	NORMAL OVARY-PS	
55-GC-PS-N	GCI-1st_del	IDUVY	NORMAL OVARY-PS	
56-GC-PS-N	GCI-4th_del	ZCXAD	NORMAL OVARY-PS	
57-GC-PS-N	GCI-4th_del	PEQ6C	NORMAL OVARY-PS	
58-GC-PS-N	GCI-1st_del	DD73B	NORMAL OVARY-PS	
59-GC-PS-N	GCI-4th_del	E2UF7	NORMAL OVARY-PS	
60-GC-PS-N	GCI-4th_del	4YG5P	NORMAL OVARY-PS	
61-GC-PS-N	GCI-1st_del	FDPL9	NORMAL OVARY-PS	
62-Bc-PM-N	BioChain	A503274	NORMAL OVARY-PM	
63-Bc-PM-N	BioChain	A504086	NORMAL OVARY-PM	
64-Ic-PM-N	Ichilov	CG-188-7	NORMAL OVARY-PM	
65-GO-SIIIC-SER	GOG	2001-12-G035	Serous adenocarcinoma	Stage 3C
66-AB-SIIIC-SER	ABS	N0021	Papillary serous adenocarcinoma	Stage 3C
67-BC-SER	BioChain	A503175	Serous papillary cystadenocarcinoma	
68-Bc-SER	Biochain	A406023	Adenocarcinoma	
69-Bc-SER	Biochain	A407068	Adenocarcinoma	
70-AB-SER	ABS	ILS-7286	Papillary cystadenocarcinoma	UN
71-AB-SER	ABS	A0106	adenocarcinoma	UN
72-AB-SER	ABS	ILS-1431	Papillary adenocarcinoma	UN
73-Bc-SER	BioChain	A503176	Serous papillary cystadenocarcinoma	
74-AB-SER	ABS	ILS-1408	Papillary adenocarcinoma	UN
75-Bc-SER	Biochain	A407069	Adenocarcinoma	
76-AB-SER	ABS	ILS-1406	Papillary adenocarcinoma	UN
77-GO-Ser Mix SIIIC-OTR	GOG	2002-05-G509	Mixed serous and endometrioid adenocarcinoma of mullerian	Stage3C
78-Bc-MUC	BioChain	A504083	Mucinous adenocarcinoma	
79-Bc-MUC	BioChain	A504084	Mucinous adenocarcinoma	
80-Bc-Car-OTR	BioChain	A407065	Carcinoma	
81-GO-Clear cell SIIIA-OTR	GOG	2001-10-G002	Clear cell adenocarcinoma	Stage 3A
82-AB-BRD	ABS	VNM-00187	Mucinous cystadenocarcinoma with low malignant	
83-GO-SIA-BRD	GOG	98-08-G001	Endometrioid adenocarcinoma of borderline malignancy	Stage 1A

TABLE 2

Breast RNA details:				
sample name	Source	sample_id	Sample DIAGNOSIS	CANCER_STAGE
1-As-DCIS S0	Asterand	19723	Ductal Carcinoma In Situ(DCIS)	STAGE 0
2-GC-IDC SI	GCI-1st_del	5IRTK	INFILTRATING DUCTAL CARCINOMA	STAGE I

TABLE 2-continued

Breast RNA details:				
sample name	Source	sample_id	Sample DIAGNOSIS	CANCER_STAGE
3-(42)-AB-IDC SI	ABS	6005020031T	INfiltrATING DUCTAL CARCINOMA	STAGE I
4-(7)-AB-IDC SI	ABS	7263T	INfiltrATING DUCTAL CARCINOMA	STAGE I
5-GC-IDC SI	GCI- 1st_del	DSI52	INfiltrATING DUCTAL CARCINOMA	STAGE I
6-GC-IDC SI	GCI- 1st_del	S2GBY	INfiltrATING DUCTAL CARCINOMA	STAGE I
7-GC-IDC SI	GCI- 1st_del	POPHP	INfiltrATING DUCTAL CARCINOMA	STAGE I
8-GC-IDC SI	GCI- 1st_del	I2YLE	INfiltrATING DUCTAL CARCINOMA	STAGE I
9-As-IDC SI	Asterand	17959	INfiltrATING DUCTAL CARCINOMA	STAGE I
10-(12)-AB-IDC SIIA	ABS	1432T	INfiltrATING DUCTAL CARCINOMA	STAGE IIA
11-As-IDC SIIA	Asterand	17138	INfiltrATING DUCTAL CARCINOMA	STAGE IIA
12-GC-IDC SIIA	GCI- 1st_del	YSZ67	INfiltrATING DUCTAL CARCINOMA	STAGE IIA
13-(6)-AB-IDC SIIA	ABS	7238T	INfiltrATING DUCTAL CARCINOMA	STAGE IIA
14-(26)-AB-IDC SIIA	ABS	7249T	INfiltrATING DUCTAL CARCINOMA	STAGE IIA
15-GC-IDC SIIA	GCI- 1st_del	UT3SE	INfiltrATING DUCTAL CARCINOMA	STAGE IIA
16-GC-IDC SIIA	GCI- 1st_del	PVSYX	INfiltrATING DUCTAL CARCINOMA	STAGE IIA
17-GC-IDC SIIA	GCI- 1st_del	GETCV	INfiltrATING DUCTAL CARCINOMA	STAGE IIA
18-(27)-AB-IDC SIIA	ABS	4907020072T	INfiltrATING DUCTAL CARCINOMA	STAGE IIA
19-GC-IDC SIIB	GCI- 1st_del	SE5BK	INfiltrATING DUCTAL CARCINOMA	STAGE IIB
20-GC-IDC SIIB	GCI- 1st_del	OLKL4	INfiltrATING DUCTAL CARCINOMA	STAGE IIB
21-GC-IDC SIIB	GCI- 1st_del	VK1EJ	INfiltrATING DUCTAL CARCINOMA	STAGE IIB
22-GC-IDC SIIB	GCI- 1st_del	3Z5Z4	INfiltrATING DUCTAL CARCINOMA	STAGE IIB
23-(13)-AB-IDC SIIB	ABS	A0133T	INfiltrATING DUCTAL CARCINOMA	STAGE IIB
24-GC-IDC SIIB	GCI- 1st_del	J5MPN	INfiltrATING DUCTAL CARCINOMA	STAGE IIB
25-GC-IDC SIIB	GCI- 1st_del	54NTA	INfiltrATING DUCTAL CARCINOMA	STAGE IIB
27-GC-IDC SIHA	GCI- 1st_del	RD3F9	INfiltrATING DUCTAL CARCINOMA	STAGE IIIA
28-(17)-AB-IDC SIHA	ABS	4904020036T	INfiltrATING DUCTAL CARCINOMA	STAGE IIIA

TABLE 2-continued

Breast RNA details:				
sample name	Source	sample_id	Sample DIAGNOSIS	CANCER_STAGE
29-(16)-AB-IDC IIIA	ABS	4904020032T	INFILTRATING DUCTAL CARCINOMA	STAGE IIIA
30-(15)-AB-IDC SIIIA	ABS	7259T	INFILTRATING DUCTAL CARCINOMA	STAGE IIIA
31-GC-IDC SIIIA	GCI- 1st_del	YOLOF	INFILTRATING DUCTAL CARCINOMA	STAGE IIIA
32-GC-IDC SIIIB	GCI- 1st_del	4W2NY	INFILTRATING DUCTAL CARCINOMA	STAGE IIIB
33-GC-IDC SIIIB	GCI- 1st_del	YQ1WW	INFILTRATING DUCTAL CARCINOMA	STAGE IIIB
34-GC-IDC SIIIB	GCI- 1st_del	KIOE7	INFILTRATING DUCTAL CARCINOMA	STAGE IIIB
35-As-ILC SI	Asterand	17090	INFILTRATING LOBULAR CARCINOMA	STAGE I
36-GC-ILC SIIA	GCI- 1st_del	I35US	INFILTRATING LOBULAR CARCINOMA	STAGE IIA
37-GC-ILC SIIIB	GCI- 1st_del	IS84Y	INFILTRATING LOBULAR CARCINOMA	STAGE IIB
38-(52)-Bc-ILC	Biochain	A605360	INFILTRATING LOBULAR CARCINOMA	
39-As-BNG	Asterand	11975	FIBROADENOMA	
40-GC-BNG	GCI- 2nd_del	ZT15M	FIBROADENOMA	
41-GC-BNG	GCI- 2nd_del	NNP3Q	FIBROADENOMA	
42-GC-BNG	GCI- 2nd_del	QK8IY	FIBROADENOMA	
43-GC-N PS	GCI- 1st_del	83LO7	NORMAL BREAST-PS	
45-GC-N PS	GCI- 2nd_del	O6JBJ	NORMAL BREAST-PS	
46-GC-N PS	GCI- 2nd_del	E6UDD	NORMAL BREAST-PS	
47-GC-N PS	GCI- 1st_del	DHLR1	NORMAL BREAST-PS	
48-GC-N PS	GCI- 2nd_del	JHQEH	NORMAL BREAST-PS	
49-(63)-Am-N PS	Ambion	26486	NORMAL BREAST-PS	
50-GC-N PS	GCI- 2nd_del	ONBFK	NORMAL BREAST-PS	
51-GC-N PS	GCI- 1st_del	TG6J6	NORMAL BREAST-PS	
52-As-N PS	Asterand	14398	NORMAL BREAST-PS	
54-GC-N PS	GCI- 2nd_del	AJGXV	NORMAL BREAST-PS	
56-GC-N PS	GCI- 1st_del	HLCZX	NORMAL BREAST-PS	
58-GC-N PS	GCI- 1st_del	FGV8P	NORMAL BREAST-PS	
59-As-N PS	Asterand	9264	NORMAL BREAST-PS	
60-(57)-Bc-N PM	Biochain	A609233	NORMAL BREAST-PM	
61-(59)-Bc-N PM	Biochain	A607155	NORMAL BREAST-PM	
62-(60)-Bc-N PM	Biochain	A609234	NORMAL BREAST-PM	
63-(66)-Am-N PM	Ambion	36678	NORMAL BREAST-PM	
64-(64)-Am-N PM	Ambion	23036	NORMAL BREAST-PM	
66-(67)-Am-N PM	Ambion	073P010602086A	NORMAL BREAST-PM	

TABLE 2-continued

Breast RNA details:				
sample name	Source	sample_id	Sample DIAGNOSIS	CANCER_STAGE
67-(58)-Bc-N PM	Biochain	A609232	NORMAL BREAST-PM	
68-As-N PM	Asterand	8862	NORMAL BREAST-PM	
69-As-N PM	Asterand	8457	NORMAL BREAST-PM	
70-(43)-Bc-IDC	Biochain	A609183	INfiltrATING DUCTAL CARCINOMA	
71-(54)-Bc-IDC	Biochain	A605353	INfiltrATING DUCTAL CARCINOMA	
72-(55)-Bc-IDC	ABS	A609179	INfiltrATING DUCTAL CARCINOMA	
73-(47)-Bc-IDC	Biochain	A609221	INfiltrATING DUCTAL CARCINOMA	
74-(48)-Bc-IDC	Biochain	A609222	INfiltrATING DUCTAL CARCINOMA	
75-(53)-Bc-IDC	Biochain	A605151	INfiltrATING DUCTAL CARCINOMA	
76-(61)-Bc-IDC	Biochain	A610029	INfiltrATING DUCTAL CARCINOMA	
77-(46)-Bc-Carci	Biochain	A609177	Carcinoma	
78-(62)-Bc-IDC	Biochain	A609194	INfiltrATING DUCTAL CARCINOMA	
79-(32)-AB-Muc Carci SIIA	Ambion	7116T	Mucinous carcinoma	STAGE IIA
80-(49)-Bc-IDC	Biochain	A609223	INfiltrATING DUCTAL CARCINOMA	
81-(45)-Bc-IDC	Biochain	A609181	INfiltrATING DUCTAL CARCINOMA	
82-(50)-Bc-IDC	Biochain	A609224	INfiltrATING DUCTAL CARCINOMA	
83-(44)-Bc-IDC	Biochain	A609198	INfiltrATING DUCTAL CARCINOMA	
84-(51)-Bc-IDC	Biochain	A605361	INfiltrATING DUCTAL CARCINOMA	
85-(31)-Ic-IDC	Ambion	CG-154	INfiltrATING DUCTAL CARCINOMA	

TABLE 3

Lung Panel RNA Details				
sample name	Source	sample_id	DIAGNOSIS	CANCER_STAGE
1-GC-BAC-SIA	GCI- 1st_del	7Z9V4	ADENOCARCINOMA	STAGE IA
2-GC-BAC-SIB	GCI- 1st_del	ZW2AQ	ADENOCARCINOMA	STAGE IB
4-GC-Adeno-SIA	GCI- 1st_del	3MOPL	ADENOCARCINOMA	STAGE IA
5-GC-Adeno-SIA	GCI- 1st_del	KOJXD	ADENOCARCINOMA	STAGE IA
6-GC-Adeno-SIA	GCI- 1st_del	X2Q44	ADENOCARCINOMA	STAGE IA
8-GC-Adeno-SIA	GCI- 1st_del	BS9AF	ADENOCARCINOMA	STAGE IA
9-GC-Adeno-SIA	GCI- 1st_del	UCLOA	ADENOCARCINOMA	STAGE IA

TABLE 3-continued

Lung Panel RNA Details				
sample name	Source	sample_id	DIAGNOSIS	CANCER_STAGE
10-GC-Adeno-SIA	GCI-1st_del	BVYK3	ADENOCARCINOMA	STAGE IA
11-GC-Adeno-SIB	GCI-1st_del	U4DM4	ADENOCARCINOMA	STAGE IB
12-GC-Adeno-SIB	GCI-1st_del	OWX5Y	ADENOCARCINOMA	STAGE IB
13-GC-Adeno-SIIA	GCI-1st_del	XYY96	ADENOCARCINOMA	STAGE IIA
14-GC-Adeno-SIIA	GCI-1st_del	SO7B1	ADENOCARCINOMA	STAGE IIA
15-GC-Adeno-SIIIA	GCI-1st_del	QANSY	ADENOCARCINOMA	STAGE IIIA
18-(76)-Bc-Adeno	Biochain	A609218	ADENOCARCINOMA	
19-As-Sq-S0	Asterand	9220	Squamous Cell Carcinoma	Occult
20-GC-Sq-SIA	GCI-1st_del	U2QHS	Squamous Cell Carcinoma	STAGE IA
21-GC-Sq-SIB	GCI-2nd_del	TRQR7	Squamous Cell Carcinoma	STAGE IB
22-As-Sq-SIB	Asterand	17581	Squamous Cell Carcinoma	STAGE IB
23-As-Sq-SIB	Asterand	18309	Squamous Cell Carcinoma	STAGE IB
24-As-Sq-SIB	Asterand	9217	Squamous Cell Carcinoma	STAGE IB
25-GC-Sq-SIIB	GCI-1st_del	RXQ1P	Squamous Cell Carcinoma	STAGE IIB
26-GC-Sq-SIIB	GCI-1st_del	KB5KH	Squamous Cell Carcinoma	STAGE IIB
27-GC-Sq-SIIIA	GCI-1st_del	LAYMB	Squamous Cell Carcinoma	STAGE IIIA
30-(19)-Bc-Sq	Biochain	A408175	Squamous Cell Carcinoma	
31-(78)-Bc-Sq	Biochain	A607125	Squamous Cell Carcinoma	
33-(80)-Bc-Sq	Biochain	A609163	Squamous Cell Carcinoma	
34-(18)-Bc-Sq	Biochain	A503387	Squamous Cell Carcinoma	
35-(81)-Bc-Sq	Biochain	A609076	Squamous Cell Carcinoma	
36-GC-LCC-SIA	GCI-1st_del	AF8AL	LARGE CELL CARCINOMA	STAGE IA
37-GC-LCC-SIB	GCI-1st_del	O62XU	LARGE CELL CARCINOMA	STAGE IB
38-GC-LCC-SIB	GCI-2nd_del	OLOIM	LARGE CELL CARCINOMA	STAGE IB
39-GC-LCC-SIIB	GCI-4th_del	1ZWSV	LARGE CELL CARCINOMA	STAGE IIB
41-GC-LCC-SIIB	GCI-1st_del	38B4D	LARGE CELL CARCINOMA	STAGE IIB
42-GC-SCC-SIB	GCI-1st_del	QPJQL	SMALL CELL CARCINOMA	STAGE IB
43-(32)-Bc-SCC	Biochain	A501391	SMALL CELL CARCINOMA	
44-(30)-Bc-SCC	Biochain	A501389	SMALL CELL CARCINOMA	
45-(83)-Bc-SCC	Biochain	A609162	SMALL CELL CARCINOMA	
46-(86)-Bc-SCC	Biochain	A608032	SMALL CELL CARCINOMA	
47-(31)-Bc-SCC	Biochain	A501390	SMALL CELL CARCINOMA	
48-(84)-Bc-SCC	Biochain	A609167	SMALL CELL CARCINOMA	
49-(85)-Bc-SCC	Biochain	A609169	SMALL CELL CARCINOMA	
50-(33)-Bc-SCC	Biochain	A504115	SMALL CELL CARCINOMA	
51-As-N-PS	Asterand	9078	Normal lung	
52-As-N-PM	Asterand	8757	Normal lung	
53-As-N-PM	Asterand	6692	Normal lung	
54-As-N-PM	Asterand	7900	Normal lung	
55-As-N-PM	Asterand	8771	Normal lung	
56-As-N-PM	Asterand	13094	Normal lung	
57-As-N-PM	Asterand	19174	Normal lung	
58-As-N-PM	Asterand	13128	Normal lung	
59-As-N-PM	Asterand	14374	Normal lung	
60-(99)-Am-N PM	Ambion	36856	Normal PM	
61-(96)-Am-N PM	Ambion	36853	Normal PM	
62-(97)-Am-N PM	Ambion	36854	Normal PM	
63-(93)-Am-N PM	Ambion	111P0103A	Normal PM	
64-(98)-Am-N PM	Ambion	36855	Normal PM	
69-(91)-Bc-N PM	Biochain	A607257	Normal (Pool 2) PM	
70-(90)-Bc-N PM	Biochain	A608152	Normal (Pool 2) PM	

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TABLE 4

Healthy panel RNA Details:		
sample name	Source	Sample id
1-Bc-Rectum	Biochain	A610297
2-Bc-Rectum	Biochain	A610298
3-GC-Colon	GCI	ZJ17R
4-GC-Colon	GCI	YUZNR
5-GC-Colon	GCI	28QN6
6-Bc-Colon	Biochain	A501156
7-GC-Small bowel	GCI	V9L7D
8-Bc-Esoph	Biochain	A603814
9-Bc-Esoph	Biochain	A603813
10-As-Panc	Asterand	8918
11-As-Panc	Asterand	10082
12-As-Liver	Asterand	7916
13-GC-Kidney	GCI	N1EVZ
14-GC-Kidney	GCI	BMI6W
15-Bc-Adrenal	Biochain	A610374
16-Am-Lung	Ambion	111P0103A
17-Bc-Lung	Biochain	A503205
18-As-Lung	Asterand	6692
19-As-Lung	Asterand	7900
20-Am-Ovary	Asterand	16848
21-GC-Ovary	GCI	Y9VHI
22-GC-Ovary	GCI	DD73B
23-GC-Ovary	GCI	FDPL9
24-GC-Cervix	GCI	E2P2N
25-ABS-Bladder	ABS	150300503
26-ABS-Bladder	ABS	150700103
27-ABS-Bladder	ABS	150700203
28-Am-Placen	Ambion	021P33A
29-Bc-Placen	Biochain	A411073
30-Am-Breast	Ambion	26486
31-Am-Breast	Ambion	23036
32-GC-Breast	GCI	E6UDD
33-Bc-Breast	Biochain	A609234
34-Am-Prostate	Ambion	25955
35-Bc-Prostate	Biochain	A609258

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TABLE 4-continued

Healthy panel RNA Details:		
sample name	Source	Sample id
36-As-Testis	Asterand	13071
37-As-Testis	Asterand	19671
38-TH-Blood-PBMC	Tel-Hashomer	52497
39-TH-Blood-PBMC	Tel-Hashomer	31055
40-TH-Blood-PBMC	Tel-Hashomer	31058
41-Ic-Spleen	Ichilov	CG-267
42-ABS-Spleen	ABS	150800704
43-ABS-Spleen	ABS	150800904
44-ABS-Spleen	ABS	150801804
45-ABS-Thymus	ABS	13066
46-ABS-Thymus	ABS	13105
47-ABS-Thymus	ABS	133968
48-Bc-Thyroid	Biochain	A610287
49-Ic-Thyroid	Ichilov	CG-119-2
50-GC-Sali gland	GCI	NNSMV
51-Ic-Cerebellum	Ichilov	CG-183-5
52-Bc-Brain	Biochain	A411322
53-Bc-Brain	Biochain	A411079
54-ABS-Heart	ABS	151101109
55-ABS-Heart	ABS	352081026
56-ABS-Heart	ABS	352JA02409
57-Ic-Heart (Fibrotic)	Ichilov	CG-255-9
58-GC-Skel Mus	GCI	T8YZS
59-GC-Skel Mus	GCI	Q3WKA
60-As-Skel Mus	Asterand	8774
61-As-Skel Mus	Asterand	10937
62-As-Skel Mus	Asterand	6692
63-ABS-Skin	ABS	151104009
64-ABS-Skin	ABS	352MC01909
65-ABS-Skin	ABS	150402309

TABLE 5

Kidney Panel RNA Details				
Sample Name	Source	Sample ID	Diagnosis	Cancer Stage
1_AB_K_PM-N	ABS	ABS150303105	Alzheimer's	
2_AB_K_PM-N	ABS	ABS151200305	Alzheimer's	
3_AB_K_PM-N	ABS	ABS151201805	Cardio Vascular Disease	
4_AB_K_PM-N	ABS	ABS24724672102	COPD	
5_AB_K_RCC_ST2aN0MX	ABS	UH1003-29	RCC	ST2aN0MX
7_AS_K_RCC_ST3aN0M1	Asterand	52813 (1066748F-3152)	RCC	ST3aN0M1
8_AS_K_RCC_ST3NXM1	Asterand	52819 (1066176F-3152)	RCC	ST3NXM1
9_OR_K_RCC_ST4N1MX	Origene	CI0000011656 (1A26)	RCC	ST4N1MX
10_OR_K_RCC_ST3aN0M1	Origene	CU0000001623 (3714)	RCC	ST3aN0M1
11_OR_K_RCC_ST3N2M1	Origene	CU00000009324 (1A1A)	RCC	ST3N2M1
12_OR_K_RCC_ST2NXMX	Origene	CX0000000190 (3D99)	RCC	ST2NXMX
13_OR_K_RCC_ST2N0M1	Origene	CU00000005834 (34DD)	RCC	ST2N0M1
14_OR_K_RCC_ST3bN0MX	Origene	CU00000000762 (374D)	RCC	ST3bN0MX
15_OR_K_RCC_ST3NXMX	Origene	CI0000016503 (3743)	RCC	ST3NXMX
16_OR_K_RCC_ST3aNXXMX	Origene	CU00000001216 (3711)	RCC	ST3aNXXMX
17_AB_K_RCC_ST2N0MX	ABS	UH1002-14	RCC	ST2N0MX
18_AB_K_RCC_ST2bN0M1	ABS	UH1007-18	RCC	ST2bN0M1
19_AB_K_PM-N	ABS	ABS150400105	ALS	

TABLE 6

Liver Panel RNA Details				
Sample Name	Source	Sample ID	Diagnosis	Cancer Stage
41_AB_L_PM-N	ABS	ABS151203707	Alzheimer's	
42_AB_L_PM-N	ABS	ABS151003509	Dementia	
43_AS_L_PM-N	Asterand	49874 (1143071F-3152)	Respiratory arrest	
44_AS_L_PM-N	Asterand	50466 (1144029F-3152)	Unknown	
45_AS_L_PM-N	Asterand	50483 (1144465F-3152)	Cardiopulmonary arrest	
46_AB_L_HCC_ST2N1MX	ABS	UH0603-43	HCC	T2N1MX
47_AB_L_HCC_ST3N0MX	ABS	UH0901-55	HCC	T3N0MX
48_AS_L_HCC_ST3N0M0	Asterand	51356 (1100251F-3152)	HCC	T3N0M0
49_AS_L_HCC_ST4NXMX	Asterand	51365 (1100271F-3152)	HCC	T4NXMX
50_AS_L_HCC_ST2N0M0	Asterand	52528 (1149074F-3152)	HCC	T2N0M0
51_OR_L_HCC_ST2N0MX	Origene	CI0000008358 (1A25)	HCC	T2N0MX
52_OR_L_HCC_ST2NXMX	Origene	CI0000009200 (14B1)	HCC	T2NXMX
53_OR_L_HCC_STXNXM1	Origene	CI0000013002 (30B6)	HCC	TXNXM1
54_OR_L_HCC_ST3NXM1	Origene	CI0000020838 (2445)	HCC	T3NXM1
55_OR_L_HCC_ST3NXMX	Origene	CU0000000996 (15F6)	HCC	T3NXMX
56_OR_L_HCC_ST3NXMX	Origene	CU00000001197 (02DE)	HCC	T3NXMX
57_OR_L_HCC_ST3NXMX	Origene	CI0000019267 (2441)	HCC	T3NXMX
58_OR_L_HCC_ST2NXMX	Origene	CU0000005407 (0F2D)	HCC	T2NXMX
59_OR_L_HCC_ST2NXMX	Origene	CU0000006675 (0F2E)	HCC	T2NXMX

TABLE 7

Housekeeping Genes								
HSKG	Accession number	HSKG Seq ID	For primer seq ID	For primer sequence	Rev primer seq ID	Rev primer sequence	Amplicon seq id	Amplicon sequence
SDHA	NM_004168	103	104	TGGGAA CAAGAG GGCATC TG	105	CCACC ACTGC ATCAA ATTCA TG	106	TGGGAACAAG AGGGCATCTG CTAAAGTTTC AGATTCCATTT CTGCTCAGTAT CCAGTAGTGG ATCATGAATTT GATGCAGTGG TGG
HPRT1	NM_000194	107	108	TGACACT GGCAAAA CAATGCA	109	GGTCCT TTTCACC AGCAAG CT	110	TGACACTGGCAA AACAATGCAGAC TTTGCTTTCTTG GTCAGGCAGTAT AATCCAAAGATG GTCAAGGTCGCA AGCTTGCTGGTGA AAAGGACC
G6PD	NM_000402	111	112	GAGGCCG TCACCAA GAACAT	113	GGACAG CCGGTC AGAGCT C	114	GAGGCCGTACC AAGAACATTAC GAGTCCTGCATG AGCCAGATAGGC TGGAACCGCATC ATCGTGGAGAAG CCCTTCGGGAGG

TABLE 7 -continued

Housekeeping Genes								
HSKG	Accession number	HSKG Seq ID	For primer seq ID	For primer sequence	Rev primer seq ID	Rev primer sequence	Amplicon seq id	Amplicon sequence
								GACCTGCAGAGC TCTGACCGGCTGT CC
UBC	BC000449	133	134	ATTTGGG TCGCGGT TCTTG	135	TGCCTT GACATT CTCGAT GGT	136	ATTTGGGTCGCGG TTCTTGTTTGTGG ATCGCTGTGATCG TCACTTGACAATG CAGATCTTCGTGA AGACTCTGACTG GTAAGACCATCA CCCTCGAGGTTGA GCCCAGTGACAC CATCGAGAATGT CAAGGCA
RPL19	NM_000981	119	120	TGGCAAG AAGAAGG TCTGGTTA G	121	TGATCA GCCCAT CTTTGAT GAG	122	TGGCAAGAAGAA GGTCTGGTTAGAC CCCAATGAGACC AATGAAATCGCC AATGCCAATCCC GTCAGCAGATCC GGAAGCTCATCA AAGATGGGCTGA TCA
PBGD	BC019323	115	116	TGAGAGT GATTGCG GTGGG	117	CCAGGG TACGAG GCTTTC AAT	118	TGAGAGTGATTC GCGTGGGTACCC GCAAGAGCCAGC TTGCTCGCATACA GACGGACAGTGT GGTGGCAACATT GAAAGCCTCGTA CCCTGG

Specific primers and amplicons used for expression analysis of LSR transcripts are provided in Table 8.

TABLE 8

LSR Primers and Amplicons									
Amplicon name	Amplicon SEQ ID NO	Amplicon sequence	Forward primer name	For primer SEQ ID NO	For primer sequence	Reverse primer name	Rev primer SEQ ID NO	Rev primer sequence	
LSR_seg2 1-24_200- 307/308_ Amplicon	137	GTCGACAAC CAGCTCAAT GCCCAGCTG GCAGCCGGG AACCAGGC TACAACCCC TACGTC GAGTGCCAG GACAGCGTG CGACCCGTC AGGGTCGTG GCCACCAAG CAGGGCAAC GCTGTG ACCCTGGGA GATTACTAC CAGGGCCGG AGGATTACC ATCACCGGA AATGCTGAC CTGACC TT	LSR_seg 21F_ 200-307	138	GTCGA CAACC AGCTC AATGC	LSR_seg2 4R_200- 308	139	AAGGT CAGGT CAGCA TTTCC	

TABLE 8 -continued

LSR Primers and Amplicons								
Amplicon name	Amplicon SEQ ID NO	Amplicon sequence	Forward primer name	For primer SEQ ID NO	For primer sequence	Reverse primer name	Rev primer SEQ ID NO	Rev primer sequence
LSR_seg2 4-36_200- 309/310_ Amplicon	140	ATGCTGACC TGACCTTTGA CCAGACGGC GTGGGGGA CAGTGGTGT GTATTACTGC TCCG TGGTCTCAG CCCAGGACC TCCAGGGGA ACAATGAGG CCTACGCAG AGCTCATCG TCCTTG GGAGGACCT CAGGGGTGG CTGAGCTCTT ACCTGG	LSR_seg 24F_ 200-309	141	ATGCT GACCT GACCT TTGAC	LSR_seg3 6R_200- 310	142	CCAGG TAAGA GCTCA GCCAC

Specific primers and amplicons used for expression analysis of TMEM25 transcript is provided in Table 9. ²⁵ SDHA (SEQ ID:103) (GenBank Accession No. NM_004168; amplicon—SDHA_Amplicon (SEQ ID: 106)),

TABLE 9

TMEM25 primers and amplicons								
Amplicon name	Amplicon SEQ ID NO	Amplicon sequence	Forward primer name	For primer SEQ ID NO	For primer sequence	Reverse primer name	Rev primer SEQ ID NO	Rev primer sequence
TMEM25_ seg_21- 27_200- 344/346_ Amplicon	123	TTCACTGTCACT GCCCATCGGGCC CAGCATGAGCTC AACTGCTCTCTG CAGGACCCAGA AGTGGCCGATCA GCCAACGCCTCT GTCATCCTTAAT GTGCAATTCAAG CCAGAGATTGCC CAAGTCGGCGCC AAGTACCAGGAA GCTCAGGGCCCA GGCCTCCTGGTT GTCCTGTTTGCC CTGGTG	TMEM25_ seg21F_ 200-344	124	TTCA CTGT CACT GCCC ATCG G	TMEM25_ seg27R_ 200-346	125	CACC AGGG CAAA CAGG ACAA C

The expression data of LSR_seg24-36_200-309/310_Amplicon (SEQ ID:140) is described in Examples 3-9 below.

Example 3

Expression of LSR_Transcripts which are Detectable by Amplicon as Depicted in Sequence Name LSR_Seg24-36_200-309/310 in Normal and Cancerous Ovary Tissues

Expression of LSR transcripts detectable by or according to LSR_seg24-36_200-309/310_Amplicon (SEQ ID:140) and primers LSR_seg24F_200-309 (SEQ ID:141) and LSR_seg36R_200-310 (SEQ ID:142) was measured by real time PCR. Non-detected samples (sample(s) no. 28) were assigned Ct value of 41 and were calculated accordingly. In parallel the expression of several housekeeping genes—

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HPRT1 (SEQ ID:107) (GenBank Accession No. NM_000194; HPRT1_Amplicon (SEQ ID:110)), and G6PD (SEQ ID:111) (GenBank Accession No. NM_000402; G6PD_Amplicon (SEQ ID:1114)) was measured similarly. For each RT sample, the expression of the above amplicon was normalized to the normalization factor calculated from the expression of these house keeping genes as described in normalization method 2 in the “materials and methods” section. The normalized quantity of each RT sample was then divided by the median of the quantities of the normal samples (sample numbers 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63 and 64, Table 1 above), to obtain a value of fold up-regulation for each sample relative to median of the normal samples.

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FIG. 12 is a histogram showing over expression of the above-indicated LSR transcripts in cancerous Ovary samples relative to the normal samples.

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As is evident from FIG. 12, the expression of LSR transcripts detectable by the above amplicon in serous carcinoma, mucinous carcinoma and adenocarcinoma samples was significantly higher than in the non-cancerous samples (sample numbers 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63 and 64, Table 1 above). Notably an over-expression of at least 5 fold was found in 21 out of 27 serous carcinoma samples, in 7 out of 9 mucinous carcinoma samples and in 7 out of 8 endometroid carcinoma samples.

Statistical analysis was applied to verify the significance of these results, as described below.

The P value for the difference in the expression levels of LSR transcripts detectable by the above amplicon in Ovary serous carcinoma samples versus the normal tissue samples was determined by T test as 2.22e-002. The P value for the difference in the expression levels of LSR transcripts detectable by the above amplicon in Ovary mucinous carcinoma samples versus the normal tissue samples was determined by T test as 6.84e-004. The P value for the difference in the expression levels of LSR transcripts detectable by the above amplicon in Ovary endometroid carcinoma samples versus the normal tissue samples was determined by T test as 4.61e-003. The P value for the difference in the expression levels of LSR transcripts detectable by the above amplicon in Ovary Adenocarcinoma samples versus the normal tissue samples was determined by T test as 5.68e-004.

Threshold of 5 fold over expression was found to differentiate between serous carcinoma and normal samples with P value of 2.59e-009 as checked by exact Fisher test. Threshold of 5 fold over expression was found to differentiate between mucinous carcinoma and normal samples with P value of 8.43e-006 as checked by exact Fisher test. Threshold of 5 fold over expression was found to differentiate between endometroid carcinoma and normal samples with P value of 2.38e-006 as checked by exact Fisher test. Threshold of 5 fold over expression was found to differentiate between Adenocarcinoma samples and normal samples with P value of 7.28e-012 as checked by exact Fisher test.

The above values demonstrate statistical significance of the results.

Primer pairs are also optionally and preferably encompassed within the present invention; for example, for the above experiment, the following primer pair was used as a non-limiting illustrative example only of a suitable primer pair: LSR_seg24F_200-309 (SEQ ID:141); and LSR_seg36R_200-310 (SEQ ID:142).

The present invention also preferably encompasses any amplicon obtained through the use of any suitable primer pair; for example, for the above experiment, the following amplicon was obtained as a non-limiting illustrative example only of a suitable amplicon: LSR_seg24-36_200-309/310_Amplicon (SEQ ID:140).

Example 4

Expression of LSR Transcripts which are Detectable by Amplicon as Depicted in Sequence Name LSR_Seg24-36_200-309/310 in Normal and Cancerous Breast Tissues

Expression of LSR transcripts detectable by or according to seg24-36FR—LSR_seg24-36_200-309/310_Amplicon (SEQ ID:140) and primers LSR_seg24F_200-309 (SEQ ID:141) and LSR_seg36R_200-310 (SEQ ID:142) was measured by real time PCR. Non-detected samples (sample(s) no. 81) were assigned Ct value of 41 and were calculated accord-

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ingly. In parallel the expression of several housekeeping genes—G6PD (SEQ ID:111) (GenBank Accession No. NM_000402; G6PD_Amplicon), PBGD (SEQ ID:115) (GenBank Accession No. BC019323; PBGD_Amplicon) RPL19 (SEQ ID:119) (GenBank Accession No. NM_000981RPL19_Amplicon) and SDHA (SEQ ID:103) (GenBank Accession No. NM_004168SDHA_Amplicon) was measured similarly. For each RT sample, the expression of the above amplicon was normalized to the normalization factor calculated from the expression of these house keeping genes as described in normalization method 2 in the “materials and methods” section. The normalized quantity of each RT sample was then divided by the median of the quantities of the normal samples (sample numbers 43, 45, 46, 47, 48, 49, 50, 51, 52, 54, 56, 58, 59, 60, 61, 62, 63, 64, 66, 67, 68 and 69, Table 2 above), to obtain a value of fold up-regulation for each sample relative to median of the normal samples.

FIG. 13 is a histogram showing over expression of the above-indicated LSR transcripts in cancerous Breast samples relative to the normal samples.

As is evident from FIG. 13, the expression of LSR transcripts detectable by the above amplicon in cancer samples was higher than in the non-cancerous samples (sample numbers 43, 45, 46, 47, 48, 49, 50, 51, 52, 54, 56, 58, 59, 60, 61, 62, 63, 64, 66, 67, 68 and 69, Table 2 above). Notably an over-expression of at least 5 fold was found in 9 out of 53 adenocarcinoma samples.

Primer pairs are also optionally and preferably encompassed within the present invention; for example, for the above experiment, the following primer pair was used as a non-limiting illustrative example only of a suitable primer pair: LSR_seg24F_200-309 (SEQ ID: 141); and LSR_seg36R_200-310 (SEQ ID: 142).

The present invention also preferably encompasses any amplicon obtained through the use of any suitable primer pair; for example, for the above experiment, the following amplicon was obtained as a non-limiting illustrative example only of a suitable amplicon: LSR_seg24-36_200-309/310_Amplicon (SEQ ID: 140).

Example 5

Expression of LSR Transcripts which are Detectable by Amplicon as Depicted in Sequence Name LSR_Seg24-36_200-309/310 in Normal and Cancerous Lung Tissues

Expression of LSR transcripts detectable by or according to seg24-36FR LSR_seg24-36_200-309/310_Amplicon (SEQ ID:140) and primers LSR_seg24F_200-309 (SEQ ID:141) and LSR_seg36R_200-310 (SEQ ID: 142) was measured by real time PCR. In parallel the expression of several housekeeping genes—HPRT1 (SEQ ID:107) (GenBank Accession No. NM_000194 HPRT1_Amplicon (SEQ ID:110)), PBGD (SEQ ID:115) (GenBank Accession No. BC019323; PBGD_Amplicon (SEQ ID:118)), SDHA (SEQ ID:103) (GenBank Accession No. NM_004168; SDHA_Amplicon (SEQ ID:106)) and Ubiquitin (SEQ ID:133) (GenBank Accession No. BC000449; Ubiquitin_Amplicon (SEQ ID:136)) was measured similarly. For each RT sample, the expression of the above amplicon was normalized to the normalization factor calculated from the expression of these house keeping genes as described in normalization method 2 in the “materials and methods” section. The normalized quantity of each RT sample was then divided by the median of the quantities of the normal samples (sample numbers 51, 52, 53, 54, 56, 57, 58, 59, 60, 61, 62, 63, 64, 69 and 70, Table 3

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above), to obtain a value of fold up-regulation for each sample relative to median of the normal samples.

FIG. 14 is a histogram showing over expression of the above-indicated LSR transcripts in cancerous Lung samples relative to the normal samples.

As is evident from FIG. 14, the expression of LSR or transcripts detectable by the above amplicon in adenocarcinoma and non-small cell carcinoma samples was significantly higher than in the non-cancerous samples (sample numbers 51, 52, 53, 54, 56, 57, 58, 59, 60, 61, 62, 63, 64, 69 and 70, Table 3 above) and was higher in a few squamous cell carcinoma samples than in the non-cancerous samples. Notably an over-expression of at least 5 fold was found in 7 out of 15 adenocarcinoma samples, in 3 out of 18 squamous cell carcinoma samples and in 10 out of 40 non-small cell carcinoma samples.

Statistical analysis was applied to verify the significance of these results, as described below.

The P value for the difference in the expression levels of *Homo sapiens* lipolysis stimulated lipoprotein receptor transcripts detectable by the above amplicon in Lung adenocarcinoma samples versus the normal tissue samples was determined by T test as 2.98e-005. The P value for the difference in the expression levels of LSR transcripts detectable by the above amplicon in Lung squamous cell carcinoma samples versus the normal tissue samples was determined by T test as 7.42e-003. The P value for the difference in the expression levels of *Homo sapiens* lipolysis stimulated lipoprotein receptor transcripts detectable by the above amplicon in Lung large cell carcinoma samples versus the normal tissue samples was determined by T test as 1.76e-002. The P value for the difference in the expression levels of *Homo sapiens* lipolysis stimulated lipoprotein receptor transcripts detectable by the above amplicon in Lung small cell carcinoma samples versus the normal tissue samples was determined by T test as 4.35e-002. The P value for the difference in the expression levels of *Homo sapiens* lipolysis stimulated lipoprotein receptor transcripts detectable by the above amplicon in Lung non-small cell carcinoma samples versus the normal tissue samples was determined by T test as 4.31e-006.

Threshold of 5 fold over expression was found to differentiate between adenocarcinoma and normal samples with P value of 3.16e-003 as checked by exact Fisher test. Threshold of 5 fold over expression was found to differentiate between non-small cell carcinoma and normal samples with P value of 2.90e-002 as checked by exact Fisher test.

The above values demonstrate statistical significance of the results.

Primer pairs are also optionally and preferably encompassed within the present invention; for example, for the above experiment, the following primer pair was used as a non-limiting illustrative example only of a suitable primer pair: LSR_seg24F_200-309 (SEQ ID: 141).; and LSR_seg36R_200-310 (SEQ ID: 142).

The present invention also preferably encompasses any amplicon obtained through the use of any suitable primer pair; for example, for the above experiment, the following amplicon was obtained as a non-limiting illustrative example only of a suitable amplicon: LSR_seg24-36_200-309/310_Amplicon (SEQ ID: 140).

Example 6

Expression of LSR Transcripts which are Detectable by Amplicon as Depicted in Sequence Name LSR_Seg24-36_200-309/310 in Different Normal Tissues

Expression of LSR transcripts detectable by or according to seg24-36FR LSR_seg24-36_200-309/310_Amplicon

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(SEQ ID: 140) and primers LSR_seg24F_200-309 (SEQ ID: 141) and LSR_seg36R_200-310 (SEQ ID: 142) was measured by real time PCR. In parallel the expression of several housekeeping genes—SDHA (SEQ ID: 103) (GenBank Accession No. NM_004168; SDHA_Amplicon (SEQ ID: 106)), HPRT1 (SEQ ID: 107) (GenBank Accession No. NM_000194; HPRT1_Amplicon (SEQ ID: 110)), and G6PD (SEQ ID: 111) (GenBank Accession No. NM_000402; G6PD_Amplicon (SEQ ID: 114)) was measured similarly. For each RT sample, the expression of the above amplicon was normalized to the normalization factor calculated from the expression of these house keeping genes as described in normalization method 2 in the “materials and methods” section. The normalized quantity of each RT sample was then divided by the median of the quantities of the Ovary samples (sample numbers 20, 21, 22 and 23, Table 4 above), to obtain a value of relative expression of each sample relative to median of the Ovary samples.

FIG. 15 is a histogram showing the expression of the above-indicated LSR transcripts in normal tissue samples relative to the ovary samples.

Example 7

Expression of LSR Transcripts which are Detectable by Amplicon as Depicted in Sequence Name LSR_Seg24-36_200-309/310 in Normal and Cancerous Kidney Tissues

Expression of LSR transcripts detectable by or according to seg24-36FR—LSR_seg24-36_200-309/310_Amplicon (SEQ ID: 140) and primers LSR_seg24F_200-309 (SEQ ID: 141) and LSR_seg36R_200-310 (SEQ ID: 142) was measured by real time PCR. In parallel the expression of several housekeeping genes—SDHA (SEQ ID: 103) (GenBank Accession No. NM_004168; SDHA_Amplicon (SEQ ID: 106)), G6PD (SEQ ID: 111) (GenBank Accession No. NM_000402; G6PD_Amplicon (SEQ ID: 114)) and PBGD (SEQ ID: 115) (GenBank Accession No. BC019323; PBGD_Amplicon (SEQ ID: 118)) was measured similarly. For each RT sample, the expression of the above amplicon was normalized to the normalization factor calculated from the expression of these house keeping genes as described in normalization method 2 in the “materials and methods” section. The normalized quantity of each RT sample was then divided by the median of the quantities of the normal samples (sample numbers 1, 2, 3, 4 and 19, Table 5 above), to obtain a value of fold up-regulation for each sample relative to median of the normal samples.

FIG. 16 is a histogram showing down regulation of the above-indicated *Homo sapiens* lipolysis stimulated lipoprotein receptor transcripts in cancerous Kidney samples relative to the normal samples.

As is evident from FIG. 16, the expression of LSR transcripts detectable by the above amplicon in cancerous Kidney samples was significantly lower than in the non-cancerous samples (sample numbers 1, 2, 3, 4 and 19, Table 5 above).

Statistical analysis was applied to verify the significance of these results, as described below.

The P value for the difference in the expression levels of LSR transcripts detectable by the above amplicon in cancerous Kidney samples versus the normal tissue samples was determined by T test as 1.25e-01.

Primer pairs are also optionally and preferably encompassed within the present invention; for example, for the above experiment, the following primer pair was used as a non-limiting illustrative example only of a suitable primer

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pair: LSR_seg24F_200-309 (SEQ ID: 141); and LSR_seg36R_200-310 (SEQ ID: 142).

The present invention also preferably encompasses any amplicon obtained through the use of any suitable primer pair; for example, for the above experiment, the following amplicon was obtained as a non-limiting illustrative example only of a suitable_seg24-36_200-309/310_Amplicon (SEQ ID:140).

Example 8

Expression of LSR Transcripts which are Detectable by Amplicon as Depicted in Sequence Name LSR_Seg24-36_200-309/310 in Normal and Cancerous Liver Tissues

Expression of LSR transcripts detectable by or according to seg24-36FR_seg24-36_200-309/310_Amplicon (SEQ ID: 140) and primers LSR_seg24F_200-309 (SEQ ID: 141) and LSR_seg36R_200-310 (SEQ ID: 142) was measured by real time PCR. In parallel the expression of several housekeeping genes—SDHA (SEQ ID:103) (GenBank Accession No. NM_004168; SDHA_Amplicon (SEQ ID: 106)), G6PD (SEQ ID:111) (GenBank Accession No. NM_000402; G6PD_Amplicon (SEQ ID:114)) and PBGD (SEQ ID: 115) (GenBank Accession No. BC019323; —PBGD_Amplicon (SEQ ID:118)) was measured similarly. For each RT sample, the expression of the above amplicon was normalized to the normalization factor calculated from the expression of these house keeping genes as described in normalization method 2 in the “materials and methods” section. The normalized quantity of each RT sample was then divided by the median of the quantities of the normal samples (sample numbers 41, 42, 43, 44 and 45, Table 6 above), to obtain a value of fold up-regulation for each sample relative to median of the normal samples.

FIG. 17 is a histogram showing the expression of the above-indicated LSR transcripts in cancerous Liver samples relative to the normal samples.

Primer pairs are also optionally and preferably encompassed within the present invention; for example, for the above experiment, the following primer pair was used as a non-limiting illustrative example only of a suitable primer pair: LSR_seg24F_200-309 (SEQ ID: 141); and LSR_seg36R_200-310 (SEQ ID: 142) reverse primer.

The present invention also preferably encompasses any amplicon obtained through the use of any suitable primer pair; for example, for the above experiment, the following amplicon was obtained as a non-limiting illustrative example only of a suitable amplicon: LSR_seg24-36_200-309/310_Amplicon (SEQ ID: 140).

Example 9

Cloning of LSR_T1_P5a ORF Fused to Flag Tag

Cloning of LSR_T1_P5a open reading frame (ORF) (SEQ ID NO 154) fused to FLAG (amino acid sequence: DYKD-DDDK, SEQ ID NO: 153) to generated LSR_P5a protein (SEQ ID NO: 11) fused to flag, was performed by PCR as described below.

A 3-step PCR reaction was performed using PfuUltra II Fusion HS DNA Polymerase (Agilent, Catalog no. 600670) under the following conditions: on the first step, 1 µl of undiluted Ovary sample (ID PZQXH) from the Ovary panel (Table 1) served as a template for a PCR reaction with 0.5 µl of each of the primers 200_369_LSR_Kozak_NheI (SEQ ID

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NO: 147) and 200_379_LSR_Rev (SEQ ID NO: 148) in a total reaction volume of 25 µl. The reaction conditions were 5 minutes at 98° C.; 35 cycles of: 20 seconds at 98° C., 30 seconds at 55° C. and 1.5 minutes at 72° C.; then 5 minutes at 72° C. The PCR product was diluted 1:20 in DDW and 1 ul was used as a template for each of the PCR reactions on step 2.

For the second step the 5' part of LSR was amplified with 0.5 ul of each of the primers 200_369_LSR_Kozak_NheI (10 µM) (SEQ ID NO: 147) and 200_371_LSR_seg36R (10 µM) (SEQ ID NO: 149) in a total reaction volume of 25 µl. The 3' part of LSR was amplified with 0.5 ul of each of the primers 200_370_LSR_seg36F (10 µM) (SEQ ID NO: 150) and 200-373_LSR_Flag_BamHI_Rev (10 µM) (SEQ ID NO: 151) in a total reaction volume of 25 µl. The reaction conditions for both reactions were 5 minutes at 98° C.; 35 cycles of: 20 seconds at 98° C., 15 seconds at 60° C. and 1.5 minutes at 72° C.; then 5 minutes at 72° C. The products of each of the reactions were separated on 1% agarose gel and purified from the gel using Qiaquick™ Gel Extraction Kit (Qiagen, Catalog no. 28706). 100 ng of the 5' product and 100 ng of the 3' product were used as a template for the third step of the PCR reaction, in which the full LSR-Flag sequence was amplified. 0.5 µl of each of the primers 200_369_LSR_Kozak_NheI (SEQ ID NO: 147) and 200-373_LSR_Flag_BamHI_Rev (SEQ ID NO: 151) in a total reaction volume of 25 µl. The reaction conditions were 5 minutes at 98° C.; 35 cycles of: 20 seconds at 98° C., 30 seconds at 55° C. and 1.5 minutes at 72° C.; then 5 minutes at 72° C. All of the primers that were used include gene specific sequences, restriction enzyme sites, Kozak sequence and FLAG tag sequence. The PCR product of step 3 was separated on 1% agarose gel. After verification of the expected band size, the PCR product was purified using QIAquick™ Gel Extraction kit.

The purified full length PCR product was digested with NheI and BamHI restriction enzymes (New England Biolabs, Beverly, Mass., U.S.A.). After digestion, the DNA was separated on a 1% agarose gel. The expected band size was excised and extracted from the gel as described above. The digested DNA was then ligated into pIRESpuo3 vector that was digested with NheI and BamHI as described above, treated with Antarctic Phosphatase (New England Biolabs, Beverly, Mass., U.S.A., Catalog no. M0289L) for 30 minutes at 37° C. and purified from 1% agarose gel using QIAquick™ Gel Extraction kit as described above. The ligation reaction was performed with T4 DNA Ligase (Promega; Catalog no. M180A).

Example 10

Cloning of LSR_T1_P5a ORF

Cloning of LSR_T1_P5a open reading frame (ORF) (SEQ ID NO: 154) was performed by PCR to generate LSR_P5a protein (SEQ ID NO: 11), as described below.

A PCR reaction was performed using PfuUltra II Fusion HS DNA Polymerase (Agilent, Catalog no. 600670) under the following conditions: 50 ng of pIRES_puro3_LSR_T1_P5a_Flag construct described above served as a template for a PCR reaction with 0.5 micro-liter of each of the primers 200_369_LSR_Kozak_NheI (SEQ ID NO: 147) and 200-372_LSR_BamHI_Rev (SEQ ID NO: 152) in a total reaction volume of 25 µl. The reaction conditions were 5 minutes at 98° C.; 35 cycles of: 20 seconds at 98° C., 30 seconds at 55° C. and 1.5 minutes at 72° C.; then 10 minutes at 72° C. All of the primers that were used include gene specific sequences, restriction enzyme sites and Kozak

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sequence. The PCR product was separated on 1% agarose gel. After verification of the expected band size, the PCR product was purified using QIAquick™ Gel Extraction kit as described above.

The purified PCR product was digested with NheI and BamHI restriction enzymes (New England Biolabs, Beverly, Mass., U.S.A.). After digestion, the DNA was separated on a 1% agarose gel. The expected band size was excised and extracted from the gel as described above. The digested DNA was then ligated into pIRESpuro3 vector that was digested with NheI and BamHI as described above, incubated with Antarctic Phosphatase (New England Biolabs, Beverly, Mass., U.S.A., Catalog no. M0289L) for 30 minutes at 37° C. and purified from 1% agarose gel using QIAquick™ Gel Extraction kit as described above. The ligation reaction was performed with T4 DNA Ligase (Promega; Catalog no. M180A).

Sequence verification of both tagged and untagged constructs described above was performed (Hylabs, Rehovot, Israel). Two nucleotides mismatches were identified, as follows: G to A at nucleic acid position 119 of SEQ ID NO: 154, and A to G at nucleic acid position 626 from SEQ ID NO: 154, resulting in a nucleic sequence set forth in SEQ ID NO: 145 for the untagged construct, and SEQ ID NO: 146 for the tagged construct; yielding a polypeptide having an amino acid mismatch I to M in amino acid position 209 in SEQ ID NO: 301, resulting in a protein having amino acid sequence set forth in SEQ ID NO: 143 for the untagged construct and SEQ ID NO: 144 for the tagged construct.

The above recombinant plasmids were processed for stable pool generation as described below.

Example 11

Establishment of a Stable Pool of Recombinant HEK293T Cells Expressing LSR_P5A_Flag_m Protein

HEK-293T cells were stably transfected with LSR_T1_P5a_Flag_m (SEQ ID NO: 146) and pIRESpuro3 empty vector plasmids as follows:

HEK-293T (ATCC, CRL-11268) cells were plated in a sterile 6 well plate suitable for tissue culture, containing 2 ml pre-warmed of complete media, DMEM [Dulbecco's modified Eagle's Media, Biological Industries (Beit Ha'Emek, Israel, catalog number: 01-055-1A)+10% FBS [Fetal Bovine Serum, Biological Industries (Beit Ha'Emek, Israel, catalog number: 04-001-1A)+4 mM L-Glutamine (Biological Industries (Beit Ha'Emek, Israel), catalog number: 03-020-1A). 500,000 cells per well were transfected with 2 µg of DNA construct using 6 µl FuGENE 6 reagent (Roche, catalog number: 11-814-443-001) diluted into 94 µl DMEM. The mixture was incubated at room temperature for 15 minutes. The complex mixture was added dropwise to the cells. The cells were placed in an incubator maintained at 37° C. with 5% CO₂ content. 48 hours after the transfection, the cells were transferred to a 75 cm² tissue culture flask containing 15 ml of selection medium: complete medium supplemented with 5 µg/ml puromycin (Sigma, catalog number P8833). Cells were placed in an incubator, and the medium was replaced every 3-4 days, until clone formation was observed.

Example 12

Analysis of the ectopic expression of LSR_P5A_Flag_m in stably-Transfected HEK293T Cells

The expression of LSR_P5a_Flag_m (SEQ ID NO 144) in stably-transfected HEK293T cells was determined by West-

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ern blot analysis of the cell lysates, using anti LSR Antibodies and anti flag antibody as indicated in Table 9.

Cells were dissociated from the plate using Cell Dissociation Buffer Enzyme-Free PBS-Based (Gibco; 13151-014), washed in Dulbecco's Phosphate Buffered Saline (PBS) (Biological Industries, 02*023-1A) and centrifuged at 1200 g for 5 minutes. Whole cell extraction was performed by resuspending the cells in 50 mM Tris-HCl pH7.4, 150 mM NaCl, 1 mM EDTA, 1% Triton X-100, supplemented with 25× complete EDTA free protease inhibitor cocktail (Roche, 11 873 580 001) and vortexing for 20 seconds. Cell extracts were collected following centrifugation at 20000 g for 20 minutes at 4° C. and protein concentration was determined with Bradford Biorad Protein Assay (Biorad cat#500-0006). Equal protein amounts were analyzed by SDS-PAGE (Invitrogen NuPAGE 4-12% NuPAGE Bis Tris, Cat#NP0335, NP0322) and transferred to Nitrocellulose membrane (BA83, 0.2 µm, Schleicher & Schuell, Cat#401385). The membrane was blocked with TTBS (Biolab, Cat#: 20892323)/10% skim milk (Difco, Cat#232100) and incubated with the indicated primary antibodies (FIG. 18) diluted in TTBS/5% BSA (Sigma-Aldrich, A4503) at the indicated concentrations (Table 9), for 16 hours at 4° C. After 3 washes with TTBS, The membrane was further incubated for 1 hour at Room Temperature with the secondary-conjugated antibodies as indicated, diluted in TTBS. Chemiluminescence reaction was performed with ECL Western Blotting Detection Reagents (GE Healthcare, Cat #RPN2209) and the membrane was exposed to Super RX Fuji X-Ray film (Catalog no. 4741008389).

FIG. 18 demonstrates the expression of LSR_P5a_Flag_m protein (SEQ ID: 144) in recombinant HEK293T cells at the expected band size ~70 kDa, as detected with anti Flag (Sigma cat#A8592) (FIG. 18A) and anti LSR antibodies as follow: Abnova, cat#H00051599-B01P (FIG. 18B) Abcam, cat ab59646 (FIG. 18C) and Sigma cat#HPA007270 (FIG. 18D).

Example 13

Determination of the Subcellular Localization of the Ectopic LSR_P5A_Flag_m in HEK293T Cells

The subcellular localization of the LSR_P5a_Flag_m protein (SEQ ID NO: 144) was determined in stably-transfected cells by confocal microscopy.

Stably transfected recombinant HEK293T cells expressing a LSR_P5a_Flag_m (SEQ ID NO: 144) described above were plated on coverslips pre-coated with Poly-L-Lysine (Sigma; Catalogue no. P4832). After 24 hrs the cells were processed for immunostaining and analyzed by confocal microscopy. The cover slip was washed in phosphate buffered saline (PBS), then fixed for 15 minutes in a solution of PBS/3.7% paraformaldehyde (PFA) (EMS, catalog number: 15710)/3% glucose (Sigma, catalog number: G5767). The PFA was Quenched with PBS/3 mM Glycine (Sigma, catalog number: G7126) for 5 minutes. After two 5-minute washes in PBS, the cells were permeabilized with PBS/0.1% Triton-X100 for 5 minutes at Room Temperature and washed twice in PBS. Then, blocking of non-specific regions was performed with PBS/5% Bovine Serum Albumin (BSA) (Sigma, catalog number: A4503) for 20 minutes. The coverslip was then incubated in a humid chamber for 1 hour with each of the primary antibodies diluted in PBS/5% BSA as indicated, followed by three 5-minute washes in PBS. The coverslips were then incubated for 30 minutes with the corresponding secondary antibody diluted in PBS/2.5% BSA at the indicated dilution.

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The antibodies and the dilutions that were used are specified in Table 9. After a prewash in Hank's Balanced Salt Solutions w/o phenol red (HBSS) (Biological Industries Catalog no. 02-016-1), the coverslip was incubated with WGA-Alexa 488 (Invitrogen, catalog number W11261) diluted 1:200 in HBSS for 10 min, washed in HBSS and incubated in BISBENZIMIDE H 33258 (Sigma, catalog number: 14530) diluted 1:1000 in HBSS. The coverslip was then mounted on a slide with Gel Mount Aqueous medium (Sigma, catalog number: G0918) and cells were observed for the presence of fluorescent product using confocal microscopy.

The subcellular localization of LSR_P5a_Flag_m is demonstrated in FIG. 19, LSR_P5a_Flag_m (SEQ ID NO: 144) is localized mainly to the cell cytoplasm, but can also be detected on the cell surface as detected with anti Flag (Sigma cat#A9594) (FIG. 19A) and anti LSR antibodies as follows: Abcam, cat ab59646 (FIG. 19B) Abnova, cat#H00051599-B01P (FIG. 19C) and Sigma cat#HPA007270 (FIG. 19D).

Example 14

Analysis of the Expression of Endogenous LSR Protein in Various Cell Lines

The expression of endogenous LSR protein in various cell lines was analyzed by Western Blotting as described below.

SK-OV3 (ATCC no. HTB-77) Caov3 (ATCC no. HTB-75), OVCAR3 (ATCC no. HTB-161), ES-2 (ATCC no. CRL-1978), OV-90 (ATCC no. CRL-11732) TOV112D (ATCC no. CRL-11731) and Hep G2 (ATCC no. HB-8065) cell extracts were prepared as described above.

HeLa (catalog no. sc-2200), MCF-7 (catalog no. sc-2206), CaCo2 (catalog no. sc-2262) and SkBR3 (catalog no. sc-2218) cell extracts were purchased from SantaCruz Biotechnology.

Equal protein amounts were analyzed by SDS-PAGE and transferred to Nitrocellulose membrane as described above. The membrane was blocked with TTBS (Biolab, Cat#: 20892323)/10% skim milk (Difco, Cat#232100) and incubated with anti LSR antibodies (Abcam, cat#ab59646) diluted in TTBS/5% BSA (Sigma-Aldrich, A4503) at the indicated concentrations (Table 9), for 16 hours at 4° C. After 3 washes with in TTBS, The membrane was further incubated for 1 hour at Room Temperature with the secondary-conjugated antibodies as indicated (Table 9), diluted in TTBS. Chemiluminescence reaction was performed with ECL Western Blotting Detection Reagents (GE Healthcare, Cat #RPN2209) and the membrane was exposed to Super RX Fuji X-Ray film (Catalog no. 4741008389).

FIG. 20 demonstrates the endogenous expression of LSR in various cell lines. A band at 72 kDa corresponding to LSR was detected with anti LSR antibody in extracts of SK-OV3, Caov3, OVCAR3, OV-90, Hep G2, HeLa, CaCo2, and SkBR3 (FIG. 20A). Anti GAPDH (Abcam cat#ab9484) served as a loading control (FIG. 20B).

TABLE 9

Primary and secondary antibodies		
Antibody	Application	Dilution
Mouse Anti FLAG-Cy3 (Sigma catalog number: A9594)	IF	1:200
Mouse Anti FLAG-HRP (Sigma Catalog no. A8592)	WB	1:2000
Rabbit Anti LSR (Abcam catalog number: ab59646)	IF	1:500
	WB	1:4000

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TABLE 9-continued

Primary and secondary antibodies		
Antibody	Application	Dilution
Rabbit Anti LSR (Sigma catalog number: HPA007270)	IF	1:100
Mouse Anti LSR (Abnova catalog number: H00051599-B01P)	WB	1:2500
Mouse Anti GAPDH (Abcam catalog number: ab9484)	IF	1:500
	WB	1:1000
Donkey Anti Rabbit Cy3 (Jackson ImmunoResearch Laboratories Inc. catalog no. 711-165-152)	WB	1:1000
Donkey Anti Mouse Dylight 549 (Jackson ImmunoResearch Laboratories Inc. catalog no. 715-506-150)	IF	1:200
	IF	1:100
Peroxidase conjugated affinity purified Goat Anti Rabbit IgG (Jackson ImmunoResearch Laboratories Inc. catalog no. 111-035-003)	WB	1:10000
Peroxidase conjugated affinity purified Goat Anti-Mouse IgG (Jackson ImmunoResearch Laboratories Inc. catalog no. 115-035-146)	WB	1:10000

Example 15

Expression of TMEM25_ Transcripts which are Detectable by Amplicon as Depicted in Sequence Name TMEM25_Seg21-27 in Normal and Cancerous Breast Tissues

Expression of TMEM25 transcripts detectable by or according to seg21-27-TMEM25_seg_21-27_200-344/346_Amplicon (SEQ ID NO: 123) and primers TMEM25_seg21F_200-344 (SEQ ID NO.124) and TMEM25_seg27R_200-346 (SEQ ID NO.125) was measured by real time PCR. In parallel the expression of several housekeeping genes—G6PD (GenBank Accession No. NM_000402; (SEQ ID NO.111) G6PD_Amplicon (SEQ ID NO.114)), RPL19 (GenBank Accession No. NM_000981; (SEQ ID NO.119)—RPL19_Amplicon (SEQ ID NO.122)), PBGD (GenBank Accession No. BC019323; (SEQ ID NO.115) PBGD_Amplicon (SEQ ID NO.118)) and SDHA (GenBank Accession No. NM_004168; (SEQ ID NO.103) SDHA_Amplicon (SEQ ID NO.106)) was measured similarly. For each RT sample, the expression of the above amplicon was normalized to the normalization factor calculated from the expression of these house keeping genes as described in "materials and methods" section. The normalized quantity of each RT sample was then divided by the median of the quantities of the normal samples (sample numbers 43, 45, 46, 47, 48, 49, 50, 51, 52, 54, 56, 58, 59, 60, 61, 62, 63, 64, 66, 67, 68 and 69, Table 1 above), to obtain a value of fold differential expression for each sample relative to median of the normal samples.

In two experiments that were carried out no differential expression in the cancerous samples relative to the normal samples was observed (FIG. 21).

Primer pairs are also optionally and preferably encompassed within the present invention; for example, for the above experiment, the following primer pair was used as a non-limiting illustrative example only of a suitable primer pair: TMEM25_seg21F_200-344 (SEQ ID NO.124) forward primer; and TMEM25_seg27R_200-346 (SEQ ID NO.125) reverse primer.

The present invention also preferably encompasses any amplicon obtained through the use of any suitable primer pair; for example, for the above experiment, the following amplicon was obtained as a non-limiting illustrative example

only of a suitable amplicon: TMEM25_seg_21-27_200-344/346_Amplicon (SEQ ID NO: 123).

Example 16

Expression of TMEM25 Transcripts which are Detectable by Amplicon as Depicted in Sequence Name TMEM25 Seg21-27 in Different Normal Tissues

Expression of TMEM25 transcripts detectable by or according to seg21-27-TMEM25_seg_21-27_200-344/346_Amplicon (SEQ ID NO: 123) and primers TMEM25_seg21F_200-344 (SEQ ID NO.124) and TMEM25_seg27R_200-346 (SEQ ID NO.125) was measured by real time PCR. In parallel the expression of several housekeeping genes—SDHA (GenBank Accession No. NM_004168; (SEQ ID NO.103) SDHA_Amplicon (SEQ ID NO.106)), G6PD (GenBank Accession No. NM_000402; (SEQ ID NO.111) G6PD_Amplicon (SEQ ID NO.114)) and HPRT1 (GenBank Accession No. NM_000194; (SEQ ID NO.107) HPRT1_Amplicon (SEQ ID NO.110)) were measured similarly. For each RT sample, the expression of the above amplicon was normalized to the normalization factor calculated from the expression of these house keeping genes as described in normalization method 2 in the “materials and methods” section. The normalized quantity of each RT sample was then divided by the median of the quantities of the Breast samples (sample numbers 30, 31, 32 and 33, Table 2 above), to obtain a value of relative expression of each sample relative to median of the Breast samples (FIG. 22).

Example 17

Cloning of TMEM25 Proteins

Cloning of TMEM25_T0_P5 ORF Fused to Flag Tag

Cloning of TMEM25_T0_P5 open reading frame (ORF) (SEQ ID NO: 130) fused to FLAG (SEQ ID NO: 153) was carried out by RT PCR as described below.

1 µl of undiluted Colon cancer pool DNA served as a template for a PCR reaction. The PCR was done using KAPA Hifi DNA polymerase (KAPABIOSYSTEM, Catalog no. KK2101) under the following conditions: 1 µl—cDNA described above; 1 µl (25 µM)—of each primer 200-374_TMEM25_NheI_Kozak_seg5F (SEQ ID NO: 127) and 200-375_TMEM25_Flag_STOP_EcoRI_seg43R (SEQ ID NO: 128) in a total reaction volume of 50 µl; with a reaction program of 5 minutes in 95° C.; 40 cycles of: 20 seconds at 98° C., 15 seconds at 55° C., 1 minute at 72° C.; then 5 minutes at 72° C. Primers which were used include gene specific sequences; restriction enzyme sites; Kozak sequence and FLAG tag.

25 µl of PCR product were loaded onto a 1.5% agarose gel stained with ethidium bromide, electrophoresed in 1×TAE solution at 100V, and visualized with UV light. After verification of expected band size. 1 µl of the PCR product above template were served as a template for reamplification. The PCR was done using KAPA Hifi DNA polymerase (KAPABIOSYSTEM, Catalog no. KK2101) under the same conditions described above.

PCR product was purified from gel using QIAquick™ Gel Extraction kit (Qiagen, catalog number: 28707).

The purified PCR product was digested with NheI and EcoRI restriction enzymes (New England Biolabs, Beverly, Mass., U.S.A.). The digested DNA was then ligated into pIRESpuo3 (pRp) vector (Clontech, cat No: 631619) previ-

ously digested with the above restriction enzymes, using T4 DNA ligase (Promega, catalog number: M1801). The resulting DNA was transformed into competent *E. Coli* bacteria DH5α (RBC Bioscience, Taipei, Taiwan, catalog number: RH816) according to manufacturer's instructions, then plated on LB-ampicillin agar plates for selection of recombinant plasmids, and incubated overnight at 37° C. The following day, positive colonies were screened by PCR using pIRE-Spuo3 vector specific primer and gene specific primer (data not shown). The PCR product was analyzed using 2% agarose gel as described above. After verification of expected band size, positive colonies were grown in 5 ml Terrific Broth supplemented with 100 µg/ml ampicillin, with shaking overnight at 37° C. Plasmid DNA was isolated from bacterial cultures using Qiaprep™ Spin Miniprep Kit (Qiagen, catalog number: 27106). Accurate cloning was verified by sequencing the inserts (Hylabs, Rehovot, Israel). Upon verification of an error-free colony (i.e. no mutations within the ORF), recombinant plasmids were processed for further analyses.

Cloning of TMEM25_T0_P5 ORF Non Tagged

Cloning of TMEM25_T0_P5 open reading frame (ORF) non tagged (SEQ ID NO: 130) was carried out by RT PCR as described below.

1 µl of undiluted Colon cancer pool DNA served as a template for a PCR reaction. The PCR was done using KAPA Hifi DNA polymerase (KAPABIOSYSTEM, Catalog no. KK2101) under the following conditions: 1 µl—cDNA described above; 1 µl (25 µM)—of each primer 200-374_TMEM25_NheI_Kozak_seg5F (SEQ ID NO: 127) and 200-377_TMEM25_STOP_EcoRI_seg43R (SEQ ID NO: 131) in a total reaction volume of 50 µl; with a reaction program of 5 minutes in 95° C.; 40 cycles of: 20 seconds at 98° C., 15 seconds at 55° C., 1 minute at 72° C.; then 5 minutes at 72° C. Primers which were used include gene specific sequences; restriction enzyme sites and Kozak sequence.

25 µl of PCR product were loaded onto a 1.5% agarose gel stained with ethidium bromide, electrophoresed in 1×TAE solution at 100V, and visualized with UV light. After verification of expected band size. 5 µl of the PCR product above template were served as a template for reamplification. The PCR was done using KAPA Hifi DNA polymerase (KAPABIOSYSTEM, Catalog no. KK2101) under the same conditions described above.

PCR product was purified from gel using QIAquick™ Gel Extraction kit (Qiagen, catalog number: 28707).

The purified PCR product was digested with NheI and EcoRI restriction enzymes (New England Biolabs, Beverly, Mass., U.S.A.). The digested DNA was then ligated into pIRESpuo3 (pRp) vector (Clontech, cat No: 631619) previously digested with the above restriction enzymes, using T4 DNA ligase (Promega, catalog number: M1801). The resulting DNA was transformed into competent *E. Coli* bacteria DH5α (RBC Bioscience, Taipei, Taiwan, catalog number: RH816) according to manufacturer's instructions, then plated on LB-ampicillin agar plates for selection of recombinant plasmids, and incubated overnight at 37° C. The following day, positive colonies were screened by PCR using pIRE-Spuo3 vector specific primer and gene specific primer (data not shown). The PCR product was analyzed using 2% agarose gel as described above. After verification of expected band size, positive colonies were grown in 5 ml Terrific Broth supplemented with 100 µg/ml ampicillin, with shaking overnight at 37° C. Plasmid DNA was isolated from bacterial cultures using Qiaprep™ Spin Miniprep Kit (Qiagen, catalog number: 27106). Accurate cloning was verified by sequencing the inserts (Hylabs, Rehovot, Israel). Upon verification of

an error-free colony (i.e. no mutations within the ORF), recombinant plasmids were processed for further analyses.

Example 18

Generation of Stable Pool Expressing TMEM25_P5 and TMEM25_P5_FLAG PROTEINS

The TMEM25_T0_P5 (SEQ ID NO: 130) and TMEM25_T0_P5_FLAG (SEQ ID NO: 126) pIRESpuro3 constructs or pIRESpuro3 empty vector were stably trans-
fected into HEK-293T cells as follows:

HEK-293T (ATCC, CRL-11268) cells were plated in a sterile 6 well plate suitable for tissue culture, using 2 ml pre-warmed of complete media, DMEM [Dulbecco's modified Eagle's Media, Biological Industries (Beit Ha'Emek, Israel, catalog number: 01-055-1A)+10% FBS [Fetal Bovine Serum, Biological Industries (Beit Ha'Emek, Israel, catalog number: 04-001-1A)+4 mM L-Glutamine (Biological Industries (Beit Ha'Emek, Israel), catalog number: 03-020-1A). 350,000 cells per well were transfected with 2 µg of DNA construct using 6 µl FuGENE 6 reagent (Roche, catalog number: 11-814-443-001) diluted into 94 µl DMEM. The mixture was incubated at room temperature for 15 minutes. The complex mixture was added dropwise to the cells and swirled. Cells were placed in incubator maintained at 37° C. with 5% CO2 content. 48 hours following transfection, transfected cells were transferred to a 75 cm2 tissue culture flask containing 15 ml of selection media: complete media supplemented with 5 µg/ml puromycin (Sigma, catalog number P8833). Cells were placed in incubator, and media was changed every 3-4 days, until clone formation observed.

Upon sufficient quantities of cells passing through selection, 3-5 million cells were harvested. Cells were lysed in 300 µl RIPA buffer (50 mM Tris HCl pH 8, 150 mM NaCl, 1% NP-40, 0.5% sodium Deoxycholate, 0.1% SDS) supplemented with protease inhibitors (Roche, catalog number: 11873580001), for 20 min at 4° C. Following centrifugation at 4° C. for 10 minutes at 14,000×rpm, the clear supernatants were transferred to clean tubes, and were used for WB procedure: 30 µg of lysate was mixed with DTT 1,4-Dithiothreitol (DTT; a reducing agent) to a final concentration of 100 mM.

In addition, the samples were then incubated at 100° C. for 10 minutes, followed by a 1 minute spin at 14,000×rpm. SDS-PAGE (Laemmli, U.K., Nature 1970; 227; 680-685) was performed upon loading of 30 µl of sample per lane into a 4-12% NuPAGE® Bis-Tris gels (Invitrogen, catalog number: NP0321), and gels were run in 1×MES SDS running buffer (Invitrogen, catalog number: NP0060), using the XCell SureLock™ Mini-Cell (Invitrogen, catalog number: E1 0001), according to manufacturer's instructions. The separated proteins were transferred to a nitrocellulose membrane (Schleicher & Schuell, catalog number: 401385) using the XCell™ II blotting apparatus (Invitrogen, catalog number E19051), according to manufacturer's instructions.

The membrane containing blotted proteins was processed for antibody detection as follows:

Non-specific regions of the membrane were blocked by incubation in 5% skim-milk diluted in Phosphate buffered saline (PBS) supplemented with 0.05% Tween-20 (PBST) for 1 hour at room temperature (all subsequent incubations occur for 1 hour at room temperature). Blocking solution was then replaced with primary Rabbit Anti TMEM25 antibody (Cat no. HPA012163, Sigma) diluted 1:500 in 5% bovine serum albumin (BSA) (Sigma, catalog number: A4503) (diluted in PBS). After 1 hour incubation, Three 5 minute washes, sec-

ondary antibody was applied: goat anti-rabbit conjugated to Peroxidase conjugated Affipure Goat anti Rabbit IgG (Jackson, catalog number: 111-035-003) diluted 1:20,000 in blocking solution. Proteins were also detected by Mouse anti Flag M2-Peroxidase (Sigma, catalog number: A8592) diluted 1:1000 in blocking solution. After 1 hour incubation, 3×5 minute washes, ECL substrate (PIERCE, catalog number: PIR-34080) was applied for 1 minute, followed by exposure to X-ray film (Fuji, catalog number: 100NIF). The results are presented in FIG. 23.

FIG. 23A demonstrate that Rabbit anti TMEM25 described above recognized specifically TMEM25_P5 protein (SEQ ID NO: 7) and TMEM25_P5_Flag (SEQ ID NO: 129) at the expected band size~40.2 kDa, but not HEK_293T_pRp3.

FIG. 23B demonstrate that TMEM25_P5_Flag proteins (SEQ ID NO: 129) were specifically recognized by anti-Flag at the expected band size~40.2 kDa.

Example 19

Determination of the Subcellular Localization of the Ectopic TMEM25_P5 and TMEM25_P5_Flag in HEK293T Cells by Immunofluorescence

Protein localization of TMEM25_P5 (SEQ ID NO: 7) and of TMEM25_P5_FLAG (SEQ ID NO: 129) were observed upon Stable transfection as described above using confocal microscopy.

Stably transfected recombinant HEK293T cells expressing TMEM25_P5 (SEQ ID NO: 7) and TMEM25_P5_FLAG (SEQ ID NO: 129) were plated on coverslips pre-coated with Poly-L-Lysine (Sigma; Catalogue no. P4832). After 24 hrs the cells were processed for immunostaining and analyzed by confocal microscopy.

The cover slip was washed in phosphate buffered saline (PBS), then fixed for 15 minutes with a solution of 3.7% paraformaldehyde (PFA) (Sigma, catalog number: P-6148) 13% glucose (Sigma, catalog number: G5767) (diluted in PBS). Quenching of PFA was done by a 5 minute incubation in 3 mM glycine (Sigma, catalog number: G7126) (diluted in PBS). After two 5-minute washes in PBS, blocking of non-specific regions was done with 5% bovine serum albumin (BSA) (Sigma, catalog number: A4503) (diluted in PBS) for 20 minutes.

The coverslip was then incubated, in a humid chamber for 1 hour, with mouse anti FLAG-Cy3 antibodies (Sigma, catalog number: A9594), diluted 1:200 in 5% BSA in PBS, OR with Rabbit Anti TMEM25 (Cat no. HPA012163, Sigma), diluted 1:50 in 5% BSA in PBS followed by three 5-minute washes in PBS. For the anti TMEM25 Ab only, a secondary Ab was needed: Donkey anti Rabbit cy3 (cat#711-165-152, Jackson) diluted 1:200 in 5% BSA in PBS, incubated in a humid chamber for 1 hour, followed by three 5-minute washes in PBS. After a prewash with BISBENZIMIDE H 33258 (HBSS) (Sigma, catalog number: 14530), the coverslip was incubated with WGA-Alexa 488 (Invitrogen, catalog number W11261) diluted 1:200 in HBSS for 10 min, followed by two washes in HBSS and incubated in BISBENZIMIDE H 33258 (Sigma, catalog number: 14530) diluted 1:1000 in HBSS. The coverslip was then mounted on a slide with Gel Mount Aqueous medium (Sigma, catalog number: G0918) and cells were observed for the presence of fluorescent product using confocal microscopy.

The subcellular localization of TMEM25_P5 (SEQ ID NO:132) and TMEM25_P5_Flag (SEQ ID NO: 129) using anti TMEM25 Abs, is demonstrated in FIGS. 24A and 24B respectively. FIG. 24C demonstrates TMEM25_P5_Flag

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(SEQ ID NO: 129) localization using anti-FLAG Abs (Sigma, catalog number: A9594). TMEM25_P5 protein is localized to the cell surface.

Example 20

Determining Cell Localization of TMEM25_P5_Flag by FACS

Membrane localization of TMEM25_P5_Flag protein (SEQ ID NO: 129) was observed upon stable transfection described above, by Flow cytometry analysis, using anti TMEM25 antibodies (Ab1628, Yomics) and by Normal mouse serum as negative control (015-000-120, Jackson). Recombinant HEK293T cells expressing TMEM25_P5_Flag were stained with anti TMEM25 antibodies (A) or by Normal mouse serum (B) followed by Donkey Anti Mouse-DyLight 549 conjugated secondary Ab (Jackson 715-506-150), and were observed for the presence of fluorescent signal.

Recombinant HEK293T-TMEM25_P5_Flag cells were dissociated from the plate using Cell dissociation buffer Enzyme-Free PBS-Based (Gibco; 13151-014), washed in FACS buffer [Dulbecco's Phosphate Buffered Saline (PBS) (Biological Industries, 02*023-1A)/1% Bovine Albumin (Sigma, A7030)] and counted. 0.5×10^6 cells were re-suspended in 100 μ l of antibody solution, at a dilution 1:2250 μ l, and incubated for 1 hour on ice. The cells were washed with ice-cold FACS buffer and incubated with secondary antibody as indicated for 1 hour on ice. The cells were washed with ice-cold FACS buffer and re-suspended in 500 μ l FACS buffer, then analyzed on the FACS machine (FACSCalibur, BD). The data was acquired and analyzed using Cellquest Pro VER. 5.2.

The results presented in FIG. 25 demonstrate that anti TMEM25 antibodies (A) bind to the full length TMEM25 protein, in HEK293T recombinant cells expressing TMEM25_P5_Flag protein, as compare to mouse serum (B) used as a negative control, indicating membrane localization of TMEM25 protein.

Example 21

Analysis of the Expression of Endogenous TMEM25 Protein in Various Cell Lines

The expression of endogenous TMEM25 protein in various cell lines was analyzed by Western Blotting as described below.

JURKAT (ATCC no. TIB-152), Daudi (ATCC no. CCL-213), RPMI8226 (ATCC no. CCL-155), G-361 (ATCC no. CRL-1424), KARPAS (ATCC no. VR-702) cell extracts were prepared as described above (Lanes 3-7 in FIG. 26—see figure legend for the corresponding lane/material assignments).

Whole cell lysates were prepared and analyzed by western blot as described above. Equal protein amounts were analyzed by SDS-PAGE and transferred to Nitrocellulose membrane as described above.

The membrane was blocked by 5% skim-milk diluted in Phosphate buffered saline (PBS) supplemented with 0.05% Tween-20 (PBST) for 1 hour incubation at room temperature (all subsequent incubations occur for 1 hour at room temperature). Blocking solution was then replaced with primary Rabbit Anti TMEM25 antibody (Cat no. HPA012163, Sigma) diluted 1:500 in 5% bovine serum albumin (BSA) (Sigma, catalog number: A4503) (diluted in PBS). After 1 hour incu-

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bation, Three 5 minute washes, secondary antibody was applied: goat anti-rabbit conjugated to Peroxidase conjugated Affipure Goat anti Rabbit IgG (Jackson, catalog number: 111-035-003) diluted 1:20,000 in blocking solution. Proteins were also detected by Mouse anti Flag M2-Peroxidase (Sigma, catalog number: A8592) diluted 1:1000 in blocking solution. After 1 hour incubation, 3x5 minute washes, ECL substrate (PIERCE, catalog number: PIR-34080) was applied for 1 minute, followed by exposure to X-ray film (Fuji, catalog number: 100NIF).

FIG. 26 demonstrates the endogenous expression of TMEM25 in various cell lines. A protein at 40.2 kDa corresponding to TMEM25 as observed in HEK293T cells expressing TMEM25_P5_Flag (lane 2; lane 1 shows a control without Flag), detected with anti TMEM25 antibody in extracts of RPMI8226 (lane 5), Daudi (lane 6) and JURKAT (lane 7).

Example 22

Transfection of Stable HEK293T_TM25 with siRNA to TMEM25

Specific knockdown of TMEM25_P5_Flag protein (SEQ ID NO:129) expression was observed in HEK293T cells stably expressing TMEM25_P5_Flag (SEQ ID NO 129) previously described upon transfection with TMEM25_P5_SiRNAs.

siRNA was purchased from Dharmacon as follows: TMEM25 (L-018183-00-0005, Dharmacon, ON TARGET plus SMART pool, Human TMEM25 (84866), 5 nmol) and scrambled SiRNA as a negative control (Dharmacon, D-001810-10-05).

Cells were plated at 50-70% confluence 24 hr prior to transfection. siRNA complexes at 250 pmol were added to 250 μ l reduced serum Opti-MEM (cat 31985, GIBCO). In parallel, Lipofectamine 2000 reagent (cat#11668019, Invitrogen) was mixed; 5 μ l was added to 250 μ l reduced serum Opti-MEM (cat 31985, GIBCO). Tubes were combined and incubated for 15-30 min at RT for sufficient complexes to form; the material was then distributed over the cells and incubated for 48 hr. Cells were harvested and cell lysates prepared as described above and detected by anti TMEM25 (Cat no. HPA012163, Sigma), following by secondary Donkey anti Rabbit conjugated to Peroxidase.

FIG. 27 demonstrates specific knockdown of TMEM25_P5_Flag protein (SEQ ID NO: 129) in HEK293T cells stably expressing TMEM25_P5_Flag (SEQ ID NO 129) transfected with TMEM25_P5 siRNA (L-018183-00-0005, Dharmacon) (Lane 2) compared to HEK293T cells stably expressing TMEM25_P5_FLAG transfected with Scrambled-SiRNA (Lane 1) (Dharmacon, D-001810-10-05), using anti TMEM25 antibodies (Sigma, cat#HPA012163).

Example 23

Immunohistochemistry (IHC) Using Anti LSR and Anti TMEM25 Poly Clonal Antibodies

To assess the tissue binding profiles, anti-LSR (Abcam catalog number: ab59646) and Anti TMEM25 (Cat no. HPA012163, Sigma), were applied on a panel of tumor tissues microarray (TMA), as detailed in Table 10.

HEK-293 cells expressing LSR_P5a_Flag_m (SEQ ID NO 144) or TMEM25_P5_Flag (SEQ ID NO:129) were used as a positive control for calibration of the pAb for staining.

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HEK293T cells transfected with empty vector were used as a negative controls as well as rabbit serum IgG antibodies.

The immunohistochemical detection of LSR_P5a_Flag_m (SEQ ID NO:144) or with TMEM25_P5_Flag (SEQ ID NO:129) by the antibodies anti-LSR and Anti TMEM25 accordingly, were calibrated in formalin-Fixed paraffin-embedded (FFPE) sections. Two antigen retrieval methods were used: pH6.1 and pH9.0 in three Abs concentrations (3.1, 0.3 ug/ml).

The antigen retrieval methods were performed as follows. The above described FFPE sections were deparaffinized, antigen retrieved and rehydrated using pH6.1 or pH9.0 Flex+ 3-in-1 antigen retrieval buffers and a PT Link automated antigen retrieval system, at 95° C. for 20 min with automatic heating and cooling.

Following antigen retrieval, sections were washed in distilled water for 2x5 min then loaded into a DAKO Autostainer Plus. The sections were then incubated for 10 min with Flex+ Peroxidase Blocking reagent, rinsed twice in 50 mM Tris.HCl, 300 mM NaCl, 0.1% Tween-20, pH 7.6 (TBST), followed by a 10 min incubation with Protein Block reagent (DAKO X0909).

The sections were incubated for 30 min with primary antibody diluted in DAKO Envision Flex antibody diluent (DAKO Cytomation, Cat #K8006). Following incubation

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with primary antibodies, the sections were then rinsed twice in FLEX buffer, incubated with anti-mouse/rabbit Flex+ HRP for 20 min, rinsed twice in FLEX buffer and then incubated with diaminobenzidine (DAB) substrate for 10 min. The chromagenic reaction was stopped by rinsing the slides with distilled water.

Following chromagenesis, the sections were counter-stained with haematoxylin, dehydrated in an ascending series of ethanols (90-99-100%), cleared in three changes of xylene and coverslipped under DePeX. Stained sections were analysed by using an Olympus BX51 microscope with a Leica DFC290 camera.

FIG. 28 demonstrates that anti LSR antibody (Cat no. ab59646, Abcam) in sections of positive control cell line (panels A, C and E) showed specific immunoreactivity in a dose dependent concentrations of 3.1 and 0.3 ug/ml respectively, as compared to the negative control cell line (panels B, D and F), in pH 9, according to the antigen retrieval method previously described.

FIG. 29 demonstrates that anti TMEM25 (Cat no. HPA012163, Sigma) in sections of positive control cell line (panels A, C and E) shows specific immunoreactivity in a dose dependent concentrations of 3.1 and 0.3 ug/ml respectively, as compared to the negative control cell line (panels B, D and F), in pH 9, according to the antigen retrieval method previously described.

TABLE 10

Summary of the tissue samples included in the tissue microarray (TMA).

TMA Map ID	(X, Y) position	Donor ID	Tissue	Path report	Age	Sex
1	(1, 1)	15766	tumour:breast:lobular carcinoma	Infiltrating lobular carcinoma. Grade2/3	42	Female
2	(2, 1)	5252	tumour:breast:ductal-adenocarcinoma	This slide contains a sample of an in situ and infiltrating ductal carcinoma (modified Bloom and Richardson grade III). Breast - in situ and infiltrating ductal carcinoma.	57	Female
3	(3, 1)	8723	tumour:breast:ductal-adenocarcinoma	Primary breast cancer (invasive ductal pattern)	74	Female
4	(4, 1)	15778	tumour:breast:lobular carcinoma	Sections of skin with dermis and subcutis infiltrated by poorly differentiated, slightly discohesive carcinoma. Individual cells have rather pleomorphic nuclei. Appearances are consistent with a pleomorphic lobular carcinoma.	52	Female
5	(5, 1)	3724	tumour:breast:ductal-adenocarcinoma	Invasive and in situ ductal carcinoma of breast.	82	Female
6	(6, 1)	2953	tumour:breast:ductal-adenocarcinoma	The specimen consists of breast tissue including DCIS (ductal carcinoma in situ) and widespread invasive poorly differentiated adenocarcinoma.	67	Female
7	(7, 1)	9533	tumour:breast:ductal-adenocarcinoma	This slide contains breast tissues infiltrated by a poorly differentiated ductal carcinoma. Breast tumour - ductal carcinoma.	50	Female
8	(8, 1)	3346	tumour:breast:ductal-adenocarcinoma	The specimen consists of connective tissue elements widely infiltrated by a poorly differentiated ductal adenocarcinoma.	63	Female
9	(9, 1)	5704	breast	This section contains a good sample of normal breast tissue	46	Female
10	(10, 1)	5347	breast	Normal breast	64	Female
11	(11, 1)	3550	tumour:colon:adenocarcinoma	The large bowel is widely infiltrated by a moderately well differentiated adenocarcinoma consistent with a derivation from the colon.	61	Male

TABLE 10-continued

Summary of the tissue samples included in the tissue microarray (TMA).						
TMA Map ID	(X, Y) position	Donor ID	Tissue	Path report	Age	Sex
12	(12, 1)	3269	tumour:colon:adenocarcinoma	Primary colonic pattern adenocarcinoma (moderately differentiated).	58	Male
13	(1, 2)	15767	tumour:colon:adenocarcinoma	Moderately differentiated adenocarcinoma.	58	Female
14	(2, 2)	3751	tumour:colon:adenocarcinoma	Moderately differentiated adenocarcinoma.	79	Female
15	(3, 2)	3881	tumour:colon:adenocarcinoma	Moderately differentiated adenocarcinoma.	71	Male
16	(4, 2)	2889	tumour:colon:adenocarcinoma	The specimen consists of large bowel showing surface ulceration associated with a moderately well differentiated primary adenocarcinoma.	73	Female
17	(5, 2)	15764	tumour:colon:adenocarcinoma	Moderately differentiated adenocarcinoma.	75	Female
18	(6, 2)	15763	tumour:colon:adenocarcinoma	Moderately differentiated adenocarcinoma.	69	Female
19	(7, 2)	2681	colon	Normal colon: full thickness.	54	Female
20	(8, 2)	3121	colon	Full thickness normal colon. Colon - normal.	34	Male
21	(9, 2)	5638	tumour:prostate	Prostate tumour - adenocarcinoma consistent with an origin in prostate. Gleason score 5 + 5 = 10.	87	Male
22	(10, 2)	15295	tumour:prostate:adenocarcinoma	Adenocarcinoma. Gleason Score 3 + 3 = 6	71	Male
23	(11, 2)	15301	tumour:prostate:adenocarcinoma	Adenocarcinoma. Gleason Score 3 + 4 = 7	51	Male
24	(12, 2)	15758	tumour:prostate:adenocarcinoma	Adenocarcinoma. Gleason Score 3 + 4 = 7	74	Male
25	(1, 3)	15745	tumour:prostate:adenocarcinoma	Adenocarcinoma. Gleason Score 4 + 5 = 9	52	Male
26	(2, 3)	15777	tumour:prostate:adenocarcinoma	Adenocarcinoma. Gleason Score 4 + 4 = 8	68	Male
27	(3, 3)	15755	tumour:prostate:adenocarcinoma	Adenocarcinoma. Gleason Score 3 + 4 = 7	55	Male
28	(4, 3)	15756	tumour:prostate:adenocarcinoma	Adenocarcinoma. Gleason Score 4 + 5 = 9	68	Male
29	(5, 3)	1317	prostate	Normal prostate	55	Male
30	(6, 3)	13951	prostate	Normal prostate	37	Male
31	(7, 3)	15052	Lymphoma	Lymph node infiltrated by large cell lymphoma	45	Female
32	(8, 3)	15760	Lymphoma	Low Grade Non-Hodgkin's Lymphoma	72	Female
33	(9, 3)	15754	Lymphoma	High Grade Non-Hodgkin's Lymphoma	77	Male
34	(10, 3)	15039	Lymphoma	Infiltrate of medium to large size lymphocytes with high mitotic rates. High grade Non-Hodgkin's Lymphoma.	47	Male
35	(11, 3)	15034	Lymphoma	Diffuse infiltrate of monotonous lymphoid cells consistent with Non-Hodgkin's Lymphoma.	71	Male
36	(12, 3)	15037	Lymphoma	Diffuse infiltrate of monotonous lymphoid cells consistent with Non-Hodgkin's Lymphoma. Thyroid tissue seen on edge of section.	53	Female
37	(1, 4)	15032	Lymphoma	Diffuse infiltrate of small lymphocytes consistent with Non-Hodgkin's Lymphoma.	50	Female
38	(2, 4)	15775	Lymphoma	Hodgkin's Lymphoma	75	Female
39	(3, 4)	4655	lymph-node	Lymph node within normal limits.	1	Female
40	(4, 4)	10789	lymph-node	Normal lymph node.	58	Male
41	(5, 4)	12053	tumour:lung	Poorly differentiated non-small cell carcinoma with some squamoid features. NON SMALL CELL CARCINOMA	72	Male
42	(6, 4)	15772	tumour:lung:non-small cell carcinoma	Poorly differentiated non-small cell carcinoma	44	Male
43	(7, 4)	13586	tumour:lung	Moderately to poorly differentiated squamous carcinoma.	67	Female

TABLE 10-continued

Summary of the tissue samples included in the tissue microarray (TMA).						
TMA Map ID	(X, Y) position	Donor ID	Tissue	Path report	Age	Sex
44	(8, 4)	2760	tumour:lung:squamous-cell-carcinoma	The specimen includes normal bronchus, a large vessel presumed to be an artery showing extensive intimal fibrosis/organisation as well as lung parenchyma widely infiltrated by a moderately well differentiated keratinising squamous cell carcinoma.	64	Male
45	(9, 4)	9354	tumour:lung:adenocarcinoma	Section of lung tissue containing a tumour growing along the alveolar spaces. The tumour is of large cell type showing features of an adenocarcinoma.	63	Male
46	(10, 4)	3473	tumour:lung:adenocarcinoma	Lung tumour - poorly differentiated adenocarcinoma consistent with a primary origin in lung if an origin elsewhere can be excluded.	72	Male
47	(11, 4)	5757	tumour:lung:adenocarcinoma	Lung tumour - adenocarcinoma of broncho-alveolar pattern.	72	Male
48	(12, 4)	4852	tumour:lung:adenocarcinoma	Lung tumour - adenocarcinoma with prominent broncho-alveolar pattern.	56	Female
49	(1, 5)	10414	small cell	Sections of lung showing a poorly differentiated, small cell carcinoma. DIAGNOSIS:	74	Male
50	(2, 5)	15055	small cell	Lung; small cell carcinoma. Fibrous tissue infiltrated by small cell carcinoma	52	Male
51	(3, 5)	15054	small cell	Sections of lung infiltrated by small cell carcinoma	65	Male
52	(4, 5)	15053	small cell	Sections of lung infiltrated by small cell carcinoma	52	Male
53	(5, 5)	1311	lung:parenchyma	Lung within normal limits.	36	Female
54	(6, 5)	14	lung:parenchyma	Normal lung and bronchus.	39	Female
55	(7, 5)	5767	lung:parenchyma	Lung parenchyma (including pleural surface) - normal limits.	45	Male
56	(8, 5)	2649	lung:parenchyma	Normal lung	37	Male
57	(9, 5)	3588	tumour:stomach	Biopsy shows poorly differentiated mucinous carcinoma.	69	Female
58	(10, 5)	5065	tumour:stomach	Sections show a well differentiated adenocarcinoma of the stomach.	64	Male
59	(11, 5)	9275	tumour:stomach	Sections of stomach antrum showing a moderately differentiated, infiltrating adenocarcinoma. The carcinoma is seen in both the mucosa and infiltrating the submucosa. DIAGNOSIS: gastric carcinoma.	78	Female
60	(12, 5)	2295	stomach	Section shows a moderately differentiated adenocarcinoma of the stomach.	66	Female
61	(1, 6)	13665	stomach:body	Full thickness section of normal stomach compatible with body.	57	Female
62	(2, 6)	2874	stomach:body	Stomach - full thickness wall with normal body type mucosa.	53	Male
63	(3, 6)	12998	tumour:ovary	A serous papillary cystic carcinoma.	78	Female
64	(4, 6)	13003	tumour:ovary	Invasive serous papillary carcinoma.	74	Female
65	(5, 6)	5739	tumour:ovary	Sections of ovary showing infiltrating islands of cohesive cells in which there are nuclei showing nuclear grooving. The appearances are consistent with a granulosa cell tumour. ovary; granulosa cell tumour.	48	Female
66	(6, 6)	9407	tumour:ovary	This slide contains a portion from the wall of a multi loculated ovarian tumour with a pattern best classified as serous cystadenocarcinoma. Ovary tumour - serous cystadenocarcinoma.	75	Female

TABLE 10-continued

Summary of the tissue samples included in the tissue microarray (TMA).						
TMA Map ID	(X, Y) position	Donor ID	Tissue	Path report	Age	Sex
67	(7, 6)	4739	ovary	This is normal ovarian tissue showing follicular structures (primordial follicles and a cystic follicle) and an involuting corpus luteum.	42	Female
68	(8, 6)	4781	ovary	Normal ovarian cortex with follicles.	34	Female
69	(9, 6)	15759	melanoma	Malignant melanoma	65	Male
70	(10, 6)	15753	melanoma	High grade malignant melanoma	46	Female
71	(11, 6)	15038	melanoma	Sections of skin with ulcerated surface with a large dermal deposit of malignant melanoma	41	Male
72	(12, 6)	15343	melanoma	Malignant melanoma	24	Male
73	(1, 7)	13779	skin	This slide contains a well orientated section of normal skin including some subcutis. Hair follicles are few in number, sebaceous glands are few and sweat glands are moderately abundant. Skin, breast - normal.	44	Female
74	(2, 7)	13280	skin	Normal skin including dermis and epidermis.	50	Female
75	(3, 7)	15342	tumour:brain:glioblastoma multiforme	Sections of brain of a very cellular tumour composed of glial cells demonstrating nuclear pleiomorphism and focal necrosis	56	Male
76	(4, 7)	9514	tumour:brain	Sections shows brain tissue infiltrated by an Astrocytoma; grade 2.	17	Male
77	(5, 7)	3306	tumour:brain	Sections show a spindle cell meningioma.	82	Male
78	(6, 7)	9516	tumour:brain	Sections shows brain tissue infiltrated by an Astrocytoma; grade 4.	25	Female
79	(7, 7)	2007	brain:cortex:frontal	Normal brain	40	Male
80	(8, 7)	4585	brain:cortex:frontal	Sections show normal grey matter of the cortex containing unremarkable neurones and this overlies normal white matter.	85	Male
81	(9, 7)	3737	tumour:kidney	normal brain cortex. The specimen shows the features of a primary renal cell adenocarcinoma.	54	Female
82	(10, 7)	13262	tumour:kidney	Grade 1 papillary transitional cell carcinoma	59	Male
83	(11, 7)	4764	tumour:kidney	Renal cell (clear cell) carcinoma	66	Male
84	(12, 7)	9043	tumour:kidney	Clear cell renal cell carcinoma of kidney.	45	Male
85	(1, 8)	2874	kidney:cortex	Normal renal cortex	53	Male
86	(2, 8)	4818	kidney:cortex	Normal renal cortex.	52	Female
87	(3, 8)	14022	tumour:liver	Poorly differentiated cholangiocarcinoma	45	Male
88	(4, 8)	15757	tumour:liver	Fibrolamellar hepatocellular carcinoma	25	Male
89	(5, 8)	14826	tumour:liver	Low Grade hepatocellular carcinoma	66	Female
90	(6, 8)	15750	tumour:liver	Cholangiocarcinoma	70	Female
91	(7, 8)	1991	liver:parenchyma	Normal liver	79	Female
92	(8, 8)	3123	liver:parenchyma	Liver - normal limits.	31	Male

Example 24

Full Length Validation of Encoding LY6G6F Transcript

A full Length transcript encoding LY6G6F (SEQ ID NO: 1) was validated as described below:

1. A reverse transcription reaction was carried out as follows: 10 µg of purified RNA (lung normal) was mixed with 150 ng Random Hexamer primers (Invitrogen, Carlsbad, Calif., USA, catalog number: 48190-011) and 500 µM dNTPs in a total volume of 156 µl. The mixture was incubated for 5

55 min at 65° C. and then quickly chilled on ice. Thereafter, 50 µl of 5× SuperscriptII first strand buffer (Invitrogen, catalog number: 18064-014, part number: Y00146), 24 µl 0.1M DTT and 400 units RNasin (Promega, Milwaukee, Wis., U.S.A., catalog number: N2511) were added, and the mixture was incubated for 10 min at 25° C., followed by further incubation at 42° C. for 2 min. Then, 10 µl (2000 units) of SuperscriptII (Invitrogen, catalog number: 18064-014) was added and the reaction (final volume of 250 µl) was incubated for 50 min at 42° C. and then inactivated at 70° C. for 15 min. The resulting cDNA was diluted 1:20 in TE buffer (10 mM Tris, 1 mM EDTA pH 8).

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2. PCR was done using 2×GoTaq ReadyMix (Promega, catalog number: M7122.) under the following conditions: 12.5 ul GoTaq ready mix; 5 ul cDNA from the above; 1 ul of 10 uM forward primer 100-690 (SEQ ID NO:51); 1 ul of 10 uM reverse primer 100-691 (SEQ ID NO:52) and 5.5 ul H₂O in a total reaction volume of 25 μl; with a reaction program of 5 minutes in 95° C.; 35 cycles of: 30 seconds at 94° C., 30 seconds at 53° C., 50 seconds at 72° C.; then 10 minutes at 72° C. The details regarding the primers are presented in Table 11 below.

The PCR product above was loaded on 1.2% agarose gel stained with ethidium bromide, electrophoresed in 1×TAE solution at 100V, and visualized with UV light. The expected band size was excised and extracted from the gel using QiaQuick™ Gel Extraction kit (Qiagen, catalog number: 28707). The purified DNA was then sequenced (Tel-Aviv University, Israel) using the above primers and was verified for the full length LY6G6F encoding transcript (SEQ ID NO:1).

Example 25

Cloning of Full Length Transcript Encoding LY6G6F Fused to EGFP

Cloning of Full Length transcript encoding LY6G6F fused to EGFP (Enhanced Green Fluorescent Protein) was performed as described below.

First, an EGFP expression vector was constructed and then the LY6G6F open reading frame (SEQ ID NO:57), encoding the amino acid sequence set forth in SEQ ID NO:58, was cloned. EGFP was subcloned into pIRESpuo3 (Clontech catalog number: 631619) as follows: EGFP-N1 vector (Clontech catalog number: 6085-1) was digested with NheI and NotI to excise the EGFP gene. The EGFP insert was then ligated into pIRESpuo3 (Clontech catalog number: 631619), which was previously digested with the same enzymes, in order to obtain the EGFP-pIRESpuo3 vector.

PCR was done using Platinum PFX™ (Invitrogen, Carlsbad, Calif., USA, catalog number: 1178-021) under the following conditions: 5 μl Platinum PFX 10× buffer; 2 μl—purified validated DNA from the above; 1 μl—10 mM dNTPs (2.5 mM of each nucleotide); 1 μl—Platinum PFX enzyme; 37 μl—H₂O; 1 μl of 10 uM forward primer 100-729 (SEQ ID NO:53); 1 μl of 10 uM reverse primer 100-730 (SEQ ID NO:54) (10 μM each) in a total reaction volume of 50 μl; with a reaction program of 5 minutes in 95° C.; 35 cycles of: 30 seconds at 94° C., 30 seconds at 55° C., 60 seconds at 68° C.; then 10 minutes at 68° C. Primers which were used included gene specific sequences corresponding to the desired coordinates of the protein and restriction enzyme sites and Kozak sequence, as listed in Table 11, below and in FIG. 6. Bold letters in Table 11 represent the specific gene sequence while the restriction site extensions utilized for cloning purposes are in Italic and Kozak sequence are underlined.

5 μl of the PCR product above, were loaded on 1.2% agarose gel stained with ethidium bromide, electrophoresed in 1×TAE solution at 100V, and visualized with UV light. After verification of expected size band, remaining PCR product was processed for DNA purification using Qiaquick PCR purification kit (Qiagen™, Valencia, Calif., U.S.A., catalog number 28106). The extracted PCR product were digested with NheI and EcoRI restriction enzymes (New England Biolabs, Beverly, Mass., U.S.A.), as listed in Table 11. After digestion, DNAs were loaded onto a 1.2% agarose gel as described above. The expected band size was excised

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and extracted from the gel using QiaQuick™ Gel Extraction kit (Qiagen, catalog number: 28707).

The digested DNA was ligated to EGFP_pIRESpuo3 vector previously digested with NheI and EcoRI restriction enzymes, using the LigaFast™ Rapid DNA Ligation System (Promega, catalog number: M8221). The resulting DNA was transformed into competent *E. Coli* bacteria DH5α (RBC Bioscience, Taipei, Taiwan, catalog number: RH816) according to manufacturer's instructions, then plated on LB-ampicillin agar plates for selection of recombinant plasmids, and incubated overnight at 37° C.

Screening positive clones was performed by PCR using GoTaq Ready Mix (Promega, catalog number: M7122). Positive colonies were grown in 5 ml Terrific Broth supplemented with 100 μg/ml ampicillin, with shaking overnight at 37° C. Plasmid DNA was isolated from bacterial cultures using Qiaprep™ Spin Miniprep Kit (Qiagen, catalog number: 27106). Accurate cloning was verified by sequencing the inserts (Tel Aviv University, Israel). Upon verification of an error-free colony (i.e. no mutations within the ORF), recombinant plasmids were processed for further analysis.

The DNA sequence of the resulting LY6G6F full length—fused to EGFP (SEQ ID NO:55) is shown in FIG. 7. In FIG. 7 gene specific sequence corresponding to the LY6G6F full length sequence is marked in bold faced type, while the EGFP sequence is marked in Italic and underlining. The amino acid sequence of the resulting LY6G6F full length fused to EGFP (SEQ ID NO:56) is shown in FIG. 8; gene specific sequence corresponding to the full length sequence of LY6G6F is marked in bold faced type, while the EGFP sequence is marked in Italic and underlining.

TABLE 11

primer details			
SEQ ID NO:	Primer ID	Primer sequence	Restriction site
51	100-690	GAGAACTTGGCAGGCTCTCC	—
52	100-691	CACACTTCCCAGCAGATGTC	—
53	100-729	CTAGCTAGCCACC <u>CATGGCAGTC</u> TTATTCTCTCTC	NheI
54	100-730	CGCGAATTGCCTGGGCTTGT GGGCAGGTG	EcoRI

Example 26

Determining Cell Localization of LY6G6F

In order to determine the cellular localization of the LY6G6F protein, LY6G6F-EGFP fusion protein (SEQ ID NO:56) was used. LY6G6F protein localization was observed upon transient transfection (Chen et al., Molecular vision 2002; 8; 372-388) using the confocal microscope. The cells were observed for the presence of fluorescent products 48 hours following transfection.

The LY6G6F-EGFP pIRESpuo3 construct, described above, was transiently transfected into HEK-293T cells as follows:

HEK-293T (ATCC, CRL-11268) cells were plated on sterile glass coverslips, 13 mm diameter (Marienfeld, catalog number: 01 115 30), which were placed in a 6 well plate, using 2 ml pre-warmed DMEM [Dulbecco's modified Eagle's Media, Biological Industries (Beit Ha'Emek, Israel),

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catalogue number: 01-055-1A]+10% FBS (Fetal Bovine Serum)+4 mM L-Glutamine. 500,000 cells per well were transfected with 2 µg of the DNA construct using 6 µl FuGENE 6 reagent (Roche, catalog number: 11-814-443-001) diluted into 94 µl DMEM. The mixture was incubated at room temperature for 15 minutes. The complex mixture was added dropwise to the cells and swirled. Cells were placed in an incubator maintained at 37° C. with 5% CO₂ content.

48 hours post transient transfection the cells were further processed for analysis in confocal microscopy. The cover slips were washed 3 times in phosphate buffered saline (PBS) and fixed for 15 minutes with 3.7% paraformaldehyde (PFA) (Sigma, catalog number: P-6148). After 2 washes in PBS, the fixed coverslips were glued to a slide using mounting solution (Sigma, catalog number: G0918) and cells were observed for the presence of fluorescent product using confocal microscope. The results are presented in FIG. 9.

FIG. 9 demonstrates that the LY6G6F_EGFP (SEQ ID NO:56) fused protein localizes to cell membrane upon expression in HEK 293T cells. The image was obtained using the 40× objective of the confocal microscope.

Example 27

Cloning and Expression of the LY6G6F, VSIG10, TMEM25 and LSR ECD-Mouse IgG2A-FC Fused Proteins

Mouse orthologs of human LY6G6F, VSIG10, TMEM25, and LSR proteins were identified using BlastP software of the National Center of Biotechnology Information (NCBI) using default parameters and used to gain experimental proof of concept related to the functionality of the LY6G6F, VSIG10, TMEM25 and/or LSR Ig fusion proteins in animal model. The mouse orthologs corresponding to human LY6G6F, VSIG10, TMEM25 and LSR proteins are shown in SEQ ID NOs: 20, 19, 9 and 21, respectively. The amino acid alignment and comparison of the human LY6G6F, VSIG10, LSR and TMEM25 proteins to the respective mouse orthologs is shown in FIGS. 5A, 5B, 5C and 5D respectively.

cDNA sequence mouse TMEM25 (SEQ ID NO:9), LY6G6F (SEQ ID NO:20), VSIG10 (SEQ ID NO:19), and LSR (SEQ ID NO: 21) proteins were each fused to the Fc domain of mouse IgG2aFc (SEQ ID NO: 27). In all cases the natural corresponding signal peptide was used for each ECD. The resulted LY6G6F, VSIG10, TMEM25 or LSR ECD-mIgG2aFc Ig fused proteins (SEQ ID NOs: 23, 24, 25, or 26, respectively) are shown in FIGS. 10A-D, respectively.

The LY6G6F, VSIG10, TMEM25 or LSR ECD-mIgG2aFc fused proteins (SEQ ID NOs: 23, 24, 25, or 26, respectively), were cloned into GPEx® retrovectors, followed by retrovector transduction into Catalent's "in-house" CHO-S cell line. A pooled population was produced and the productivity was validated. The pool was then expanded and relative productivity and relative copy number of the pool was determined. Cell culture supernatants were analyzed by Catalent's Fc ELISA assay to confirm production of LY6G6F, VSIG10, TMEM25 or LSR ECD-mIgG2aFc fused proteins.

Protein solutions were tested for bioburden and endotoxin. Human fusion proteins composed of the human ECD of either of LY6G6F, VSIG10, TMEM25 or LSR ECD fused to human IgG1 (as depicted on FIG. 11) were also expressed using a similar system.

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Assessment of the effect of LY6G6f, VSIG10, TMEM25 or LSR ECD-Ig Fusion Proteins on Mouse and Human T Cell Activation In Vitro:

Example 28

Effect of LY6G6f, VSIG10, TMEM25 or LSR ECD-Ig fusion proteins on Activation of DO11.10 Naïve Cd4+ T Cells with Ova Peptide

Naïve CD4⁺ T cells were isolated from spleens of five DO11.10 mice (Jackson) via automax sort: CD4-negative sort (Miltenyi Cat#130-095-248), including anti-CD25 (Miltenyi Cat#130-091-072) in the negative sort cocktail, followed by CD62L-positive sort (Miltenyi Cat #130-049-701). Balb/c total splenocytes were also collected from one mouse, and irradiated with 3000 rads to serve as antigen presenting cells (APCs) for the DO11.10 CD4⁺ T cells. Naïve CD4⁺ T cells were cultured at 5×10⁵ cells per well in flat-bottom 96-well plates with irradiated APCs at a ratio of 1:1 (APCs to T cells) in 200 µl of HL-1 medium, and activated with 20 µg/ml or 2 µg/ml OVA323-339 in the presence of either TMEM25-ECD-Ig (SEQ ID NO:25), LSR-ECD-Ig (SEQ ID NO:26), LY6G6F-ECD-Ig (SEQ ID NO:23) at the indicated concentrations. As positive controls, B7-H4-Ig (R&D Systems) or CTA4-Ig (mouse ECD fused to mIgG2a Fc) were used. Isotype control Ig (mIgG2a, BioXCell Cat. #BE0085) was used as a negative control. The cells were pulsed with 1 µCi of tritiated-thymidine at 24 hours, and harvested at 72 hours.

As shown in FIG. 30, TMEM25-ECD-Ig, LSR-ECD-Ig and LY6G6F-ECD-Ig elicit dose dependent inhibition of T cell activation. This was demonstrated as inhibition of T cell proliferation which was induced by OVA323-339 at 20 µg/ml (FIGS. 30 A-C, E) or 2 µg/ml (FIG. 30 D).

VSIG10-ECD-Ig fusion protein (SEQ ID NO:24) did not show activity in three experiments carried out in similar assay.

Example 29

Effect of LY6G6f, VSIG10, TMEM25 or LSR ECD-Ig Fusion Proteins on Activation of Naïve Cd4+ T Cells with anti-Cd3/anti-Cd28 Coated Beads

Naïve CD4⁺ T cells were isolated from 5 SJL (Harlan) mice via automax sort as described in the previous section. Beads were coated with anti-CD3 (0.5 µg/ml; clone 2C11) and anti-CD28 (2 µg/ml; clone 37.51 eBioscience) following manufacturer's protocol (Dynabeads M-450 Epoxy Cat. 140.11, Invitrogen), and with increasing concentrations of LSR-ECD-Ig or mIgG2a isotype control (mIgG2a, BioXCell Cat. #BE0085) (0.1-10 µg/ml). The total amount of protein used for beads coating with LSR-ECD-Ig was completed to 10 µg/ml with Control Ig. Naïve CD4⁺ T cells (0.5×10⁶/well) were activated with the coated beads at a ratio of 1:2 (beads to T cells). The cells were pulsed with 1 µCi of tritiated-thymidine after 24 hours, and harvested after 72.

LSR-ECD-Ig (SEQ ID NO:26) pronouncedly inhibited proliferation of T cell proliferation and elicit its effect in a dose dependent manner (FIG. 31).

TMEM25, LY6G6F and VSIG10 ECD Ig fusion proteins shown in FIGS. 10 and 11 are tested in a similar assay with similar results.

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Example 30

Dose Response Effect of LY6G6f, VSIG10, TMEM25 or LSR ECD-Ig Fusion Proteins on Mouse Cd4+ T Cell Activation with Plate Bound Anti-CD3, as Manifested in Cytokine Production and Expression of the Activation Marker CD69

Untouched CD4+CD25⁻ T cells were isolated from pools of spleen and lymph node cells of BALB/C mice by negative selection using CD4+CD62L+ T cell isolation Kit (Miltenyi Cat#130-093-227) according to the manufacturer's instructions. The purity obtained was >95%.

Tissue culture 96-well plates were coated overnight at 4° C. with 2 µg/ml anti-CD3 mAb (clone 145-2C11) in the presence of LY6G6F, VSIG10, TMEM25 and LSR ECD-Ig fusion proteins (SEQ ID NOs: 23, 24, 25 and 26, respectively) at 1, 5 and 10 µg/ml. Control mIgG2a (Clone C1.18.4 from BioXCell; Cat#BE0085) was added to each well in order to complete a total protein concentration of 12 µg/ml per well. Wells were plated with 1×10⁵ CD4+CD25⁻ T cells per well. At 48 hrs post stimulation, culture supernatants were collected and analyzed using mouse IFN γ ELISA kit, and cells were analyzed for expression of the activation marker CD69 by flow cytometry.

The results shown in FIG. 32 demonstrate inhibitory effects of LY6G6F, VSIG10, TMEM25 and LSR ECD-Ig fusion proteins on CD4 T cell activation, manifested by reduced IFN γ secretion (FIG. 32A) and reduced expression of CD69 (FIG. 32B) upon TCR stimulation, compared to control mIgG2a and CTLA4-Ig.

Example 31

The Effect of LY6G6f, VSIG10, TMEM25 or LSR ECD-Ig Fusion Proteins On CD4+ T Cell Differentiation In Vitro

To test the ability of LY6G6F, VSIG10, TMEM25 and LSR Ig fusion proteins to inhibit CD4+ T cell differentiation, naïve CD4+ T cells are isolated from D011.10 mice, which are transgenic for a T cell receptor (TCR) that is specific for OVA323-339 peptide. Using D011.10 T cells enables studying both polyclonal (anti-CD3/anti-CD28 mAbs) and peptide-specific responses on the same population of CD4+ T cells. Naïve CD4+ T cells are isolated from D011.10 mice and activated in culture in the presence of anti-CD3/anti-CD28 coated beads or OVA323-339 peptide plus irradiated BALB/c splenocytes, in the presence of LY6G6F, VSIG10, TMEM25 or LSR ECD-Ig fusion proteins, control Ig, or B7-H4 Ig. The cells are activated in the presence of Th driving conditions as follows: Th0 cell-(IL-2), Th1 cell-(IL-2+IL-12), Th2 cell-(IL-2+IL-4), or Th17 cell-(TGF- β +IL-6+IL-23+anti-IL-2). The effects on T cell differentiation and Th-specific responses are assessed by measuring cell proliferation and subtype specific cytokine production: IL-4, IL-5, IL-10, IL-17, IFN- γ .

Example 32

Assessment of the Effect of LY6G6f, VSIG10, TMEM25 or LSR ECD Ig Fusion Proteins on Human T Cells Activation

The effect of LY6G6F, VSIG10, TMEM25 or LSR ECD Ig fusion proteins on human T cell response is tested by two different in vitro assays using purified human T cells. In the first assay, human T cells are activated by anti-CD3 and

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anti-CD28 coated beads, and in the other assay, activation is carried out using anti-CD3 and anti-CD28 antibodies in the presence of autologous, irradiated PBMCs. The regulatory activity of LY6G6F, VSIG10, TMEM25 or LSR ECD Ig fusion proteins on human T cell activation, is evaluated by measuring cell proliferation and cytokine release.

Study I—Activation of Human T Cells with Anti-CD3 and Anti-CD28-Coated Beads is Inhibited by Fusion Proteins

Naïve CD4+ T cells are isolated from 4 healthy human donors and activated with anti-CD3 mAb/anti-CD28 mAb coated beads in the presence of control mIgG2a, or any one of the LY6G6F, VSIG10, TMEM25 or LSR ECD Ig fusion proteins. Two side-by-side culture sets are set up; one culture being pulsed at 24 hours with tritiated-thymidine and harvested at 72 hours while the second plate is harvested at 96 hours for cytokine production via LiqueChip.

Study II—Activation of Human T Cells with Irradiated Autologous PBMCs is Inhibited by Fusion Proteins

Total PBMCs are isolated from fresh blood of healthy human donors using ficoll gradient. 10×10⁶ total PBMCs are resuspended in Ex-Vivo 20 medium, and irradiated at 3000 rad. These cells are used to activate the isolated T cells in vitro, by presenting the anti-CD3, anti-CD28 and either of the test proteins. The rest of PBMCs are used for isolation of T cells using CD4+ T cell Isolation Kit II from Miltenyi.

For activation, 5×10⁵ isolated T cells are cultured in the presence of 5×10⁵ autologous irradiate PBMCs. Anti-CD3 (0.5 µg/ml), anti-CD28 (2 µg/ml) and either of LY6G6F, VSIG10, TMEM25 or LSR ECD Ig fusion proteins or control Ig (mIgG2a) are added in a soluble form. The cultures are pulsed with 1 uCi of tritiated thymidine at 24 hrs, and proliferation is measured at 72 hours.

Example 33

The Effect of LY6G6F, TMEM25 and LSR Proteins Upon Ectopic Expression in APC-Like Cells, on Human T Cell Responses

The effects of LY6G6F, TMEM25 and LSR on human T cell responses were evaluated following their ectopic expression in 'T cell stimulator' cells: a murine thymoma cell line, Bw5147, which were engineered to express membrane-bound anti-human CD3 antibody fragments, that can trigger the TCR-complex on human T cells, with or without co-expression of putative costimulatory or coinhibitory ligands.

Codon-optimized cDNAs encoding LY6G6F (SEQ ID NO: 1), TMEM25 (SEQ ID NO: 7) and LSR (SEQ ID NO: 11) were gene-synthesized and directionally cloned into a retroviral vector pCJK2 via Sfi-I sites. Monocistronic expression constructs were generated. The constructs were validated by agarose gel electrophoresis and were expressed in Bw5147 cells displaying high levels of membrane bound anti-CD3 antibody (Bw-3/2) (Leitner et al., 2010). As negative control Bw5147 cells transduced with "empty" vector (pCJK2) were used. In addition, Bw-3/2 cells expressing costimulatory molecules (ICOSL and CD70) and Bw-3/2-cells expressing coinhibitory molecules (B7-H3 and B7-H1/PD-L1) were also used as controls. Homogenously high expression of the stimulating membrane-bound anti-CD3 antibody was confirmed by FACS using a DyLight-649 anti-mouse IgG (H+L) antibody that reacts with the murine single chain antibody expressed on the stimulator cells. Presence and high level transcription of expression monocistronic constructs in the respective stimulator cells was confirmed by qPCR.

T cells were purified from buffy coats or heparinised blood derived from healthy volunteer donors and the mononuclear fraction was obtained by standard density centrifugation using Ficoll-Paque (GE-Healthcare). Untouched bulk human T cells were obtained through MACS-depletion of CD11b, CD14, CD16, CD19, CD33 and MHC-class II-bearing cells with the respective biotinylated mAb in conjunction with paramagnetic streptavidin beads (Leitner et al., 2009). Purified CD8 T cells and CD4 T cells were obtained by adding biotinylated CD4 and CD8 mAb to the pools. Naïve CD4 T cells were isolated using the Naïve CD4+ T cell Isolation Kit II (Miltenyi Biotec). Following isolation, cells were analyzed for purity by FACS, and samples with sufficient purity (>90%) were used for the experiments.

The stimulator cells were harvested, counted, irradiated (2×3000 rad) and seeded in flat-bottom 96-well plates (20000 cells/well). Liquid nitrogen stored MACS-purified T cells were thawed, counted and added to the wells at 100,000 cells per well; total volume was 200 µl/well. Triplicate wells were set up for each condition. Following 48 hours of co-culture, ³H-thymidine (final concentration of 0.025 mCi; PerkinElmer/NewEngland Nuclear Corporation, Wellesley, Mass.) was added to the wells. Following further culturing for 18 hours, the plates were harvested on filter-plates and incorporation of ³H-Thymidine was determined as described in Pfistershammer et al., 2004. In addition, a series of experiments with MACS-purified T cell subsets (CD8 T cells, CD4 T cells, and naïve CD45RA-positive CD4 T cells) were performed. Additional controls in all experiments included wells with stimulator cells alone to assess the cells microscopically and also to determine basal ³H-Thymidine incorporation of the stimulator cell w/o T cells. Results with stimulator cells that quickly disintegrated following irradiation were excluded from the analysis.

Results shown in FIG. 33 are an average of several experiments, and show the effect of stimulator cells expressing LY6G6F, TMEM25 or LSR on the proliferation of human bulk T cells (FIG. 33A), CD4+ T cells (FIG. 33B), CD8+ T cells (FIG. 33C), or naïve CD4 CD45RA+ T cells (FIG. 33D). Expression of control costimulatory molecules (ICOSL and CD70) resulted in a consistent and pronounced stimulation of proliferation of all cell subtypes. Similarly to expression of control coinhibitory molecules (B7-H3 and B7-H1/PD-L1), which resulted in a mild inhibition of proliferation of different T cell subtypes, expression of LY6G6F, TMEM25 and LSR also resulted in a mild inhibition of T cell proliferation, with the most pronounced inhibitory effects exhibited on CD8+ T cells.

Example 34

Characterizing the Target Cells for LY6G6F, VSIG10, TMEM25 And/or LSR Proteins by Determining their Binding Profile to Immune Cells

Splenocytes from D011.10 mice (transgenic mice in which all of the CD4+ T cells express a T cell receptor that is specific for OVA323-339 peptide) are activated in the presence of OVA323-339 peptide, and cells are collected at t=0, 6, 12, 24, and 48 hours following initial activation to determine which cell type is expressing a receptor for LY6G6F, VSIG10, TMEM25 and/or LSR over time. Cells are then co-stained for CD3, CD4, CD8, B220, CD19, CD11b, and CD11c.

Example 35

Assessment of the Effect of LY6G6F, VSIG10, TMEM25 or LSR ECD Ig Fusion Proteins on the Ability of B Cells to Class-Switch and Secrete Antibody

Resting B cells are isolated from unprimed C57BL/6 mice and activated in vitro in the presence of anti-CD40 plus (i) no exogenous cytokine, (ii) IL-4, or (iii) IFN-γ. The cell cultures receive control Ig (mIgG2a), anti-CD86 mAb (as a positive control for increased Ig production), or any one of LY6G6F, VSIG10, TMEM25 and LSR ECD fusion proteins described in Example 5 herein, at the time of culture set up, and are cultured for 5 days. The LY6G6F, VSIG10, TMEM25 and LSR ECD fusion proteins are tested at three concentrations each. At the end of culture, supernatants are tested for the presence of IgM, IgG1, and IgG2a via ELISA. If there appears to be an alteration in the ability of the B cells to class-switch to one isotype of antibody versus another, then the number of B cells that have class switched is determined via ELISPOT. If there is an alteration in the number of antibody producing cells, then it is determined if there is an alteration in the level of γ1- and γ2a-sterile transcripts versus the mature transcripts for IgG1 and IgG2a. Assessment of the therapeutic effect of LY6G6F, VSIG10, TMEM25 or LSR ECD Ig Fusion Proteins for Treatment of Autoimmune Diseases

Example 36

Efficacy of LY6G6F, VSIG10, TMEM25 or LSR ECD Ig Fusion Proteins in Mouse R-EAE Model of Multiple Sclerosis

The therapeutic effect of TMEM25-ECD-Ig, LSR-ECD-Ig and VSIG10-ECD-Ig fusion proteins (SEQ ID NOs: 25, 26 and 24, respectively) for treatment of autoimmune diseases was tested in a mouse model of Multiple Sclerosis; Relapsing Remitting Experimental Autoimmune Encephalomyelitis (R-EAE):

Female SJL mice 6 weeks old were purchased from Harlan and maintained in the CCM facility for 1 week prior to beginning the experiment. Mice were randomly assigned into groups of 10 animals and primed with 50 µg PLP139-151/CFA on day 0. Mice received 6 i.p. injections of 100 µg/dose of TMEM25-ECD-Ig (SEQ ID NO: 25), LSR-ECD-Ig (SEQ ID NO: 26), mIgG2a isotype control, or CTLA4-Ig (mouse ECD fused to mouse IgG2a Fc) as positive control. Treatments began at the time of onset of disease remission and were given 3 times per week for 2 weeks. Mice were followed for disease symptoms. On day 35, (during the peak of disease relapse) 5 mice of each group were assayed for DTH (delayed type hypersensitivity) response to disease inducing epitope (PLP139-151) and to relapse-associated myelin epitope (PLP178-191) via injection of 10 µg of PLP139-151 in one ear and PLP178-191 into the opposite ear. The level of ear swelling was assayed at 24 hours post challenge.

The present Example shows a pronounced decrease in disease severity of R-EAE-induced mice upon treatment with TMEM25-ECD-Ig (SEQ ID NO: 25) or LSR-ECD-Ig (SEQ ID NO: 26), in a therapeutic mode with 100 µg/dose at 3 times per week, as shown in FIG. 34A. The level of inhibition was similar to that of CTLA4-Ig.

In addition, treatment of R-EAE mice with TMEM25-ECD-Ig (SEQ ID NO: 25) or LSR-ECD-Ig (SEQ ID NO: 26) dramatically inhibited DTH responses to the disease inducing

epitope (PLP139-151) and to relapse-associated epitope (PLP178-191) at day 35 (FIG. 34B).

To test the dose dependency of the efficacy of TMEM25-ECD-Ig (SEQ ID NO: 25) as well as its mode of action in the PLP-induced R-EAE model, disease was induced as described above and mice were treated from onset of disease remission with 100, 30 or 10 ug/dose TMEM25-ECD-Ig, 3 times per week over two weeks. TMEM25-ECD-Ig decreased the level of disease severity in a dose dependent manner as shown by the milder effect observed by the lowest dose tested (10 ug/dose), which is significantly different from the effect of the high dose (100 ug/dose) (FIG. 35A). TMEM25-ECD-Ig also inhibited DTH responses to spread epitopes PLP178-191 and MBP84-104 on days 45 and 76 (FIG. 35B). Furthermore, TMEM25-ECD-Ig inhibited recall responses of day 45 and day 76 splenocytes and day 45 cervical lymph node cells, to PLP139-151, PLP178-191 and MBP84-104 (FIGS. 35C and 35D). This was manifested mainly in inhibition of proliferation as well as reduction in IFN γ and IL-17 release. TMEM25-ECD-Ig also inhibits IL-4 and IL-10 release from cervical lymph node cells of mice treated at 30 ug/dose TMEM25-ECD-Ig. There was no consistent effect on IL-4 and IL-10 release from splenocytes under these conditions.

The beneficial effect of TMEM25-ECD-Ig (SEQ ID NO: 25) in the R-EAE model was also accompanied by a significant reduction in the infiltration of immune cells to the CNS (FIG. 35E). Although none of the lineages tested in the CNS was significantly changed, there was a clear trend for reduction in CD4 $^{+}$ T cells and Dc (CD11C $^{+}$) and some increase in the B cell (CD19 $^{+}$) population, although this did not reach statistical significance (FIG. 35E).

VSIG10-ECD-Ig (SEQ ID NO: 24) was also tested in the PLP-induced R-EAE model described above. Treatments began on the day of onset of remission and given at 100 ug/dose 3 \times /week over 2 weeks. VSIG10-ECD-Ig significantly reduced disease severity as manifested in reduction in disease score (FIG. 36A). The beneficial effect of VSIG10-ECD-Ig in this model was also accompanied by inhibition of day 45 and day 76

DTH responses to spread epitopes PLP178-191 and to MBP84-104 (FIG. 36B). In addition, VSIG10-ECD-Ig (SEQ ID NO: 24) inhibited recall responses of splenocytes and draining (cervical) lymph node cells taken on day 45, in response to activation with inducing epitope PLP139-151, or spread epitopes PLP178-191 and MBP84-104 (FIGS. 36C and 36D). This was manifested in inhibition of cell proliferation as well as secretion of IFN γ , IL-17, IL-4 and IL-10.

Interestingly, on day 76 VSIG10-ECD-Ig (SEQ ID NO: 24) inhibited only MBP84-104 induced splenocytes proliferation, but not proliferation induced by the earlier myelin epitopes, (FIG. 36C). VSIG10-ECD-Ig treatment in the R-EAE model also significantly reduced the infiltration of immune cells to the CNS which was accompanied by evident but not significant elevation in the number of cells in the lymph nodes, (FIG. 36E). The major cell subtype that was reduced in the CNS was CD4 $^{+}$ T cells, however, there was also a clear trend of reduction of CD19 $^{+}$ B cells and CD11c $^{+}$ Dcs in the CNS. All these immune cell subtypes were significantly elevated in the lymph nodes, suggesting that VSIG10-ECD-Ig may inhibit trafficking of immune cells from the lymph nodes to the CNS.

LY6G6F-ECD-Ig fusion protein is studied in a similar model of Multiple Sclerosis.

Efficacy of LY6G6F, VSIG10, TMEM25 or LSR ECD Ig Fusion Proteins in Mouse CIA Models of Rheumatoid Arthritis

Study I:

LSR-ECD-Ig (SEQ ID NO: 26) was tested in mouse model of collagen-induced arthritis (CIA) which is a model of rheumatoid arthritis. Male DBA/1 mice were housed in groups of 8-10, and maintained at 21 $^{\circ}$ C. \pm 2 $^{\circ}$ C. on a 12 h light/dark cycle with food and water ad libitum. Arthritis was induced by immunisation with type II collagen emulsified in complete Freund's adjuvant. Mice were monitored on a daily basis for signs of arthritis. On the appearance of arthritis (day 1) treatment with LSR-ECD-Ig (SEQ ID NO: 26), mIgG2a isotype control or CTLA4-Ig (mouse ECD fused to mouse IgG2a Fc) as positive control (100 ug/dose, each) was initiated and given 3 times per week for 10 days. Hind footpad swelling was measured (using microcalipers), as well as the number and degree of joint involvement in all four limbs. This yielded two measurements, clinical score and footpad thickness that can be used for statistical assessment.

At the end of the treatment period mice were bled and sacrificed. For histological analysis, paws were removed at post mortem, fixed in buffered formalin (10% v/v), then decalcified in EDTA in buffered formalin (5.5% w/v). The tissues are then embedded in paraffin, sectioned and stained with haematoxylin and eosin. The scoring system is as follows:

0=normal; 1=synovitis but cartilage loss and bone erosions absent or limited to discrete foci; 2=synovitis and significant erosions present but normal joint architecture intact; 3=synovitis, extensive erosions, joint architecture disrupted.

The present Example shows that treatment of mice with established CIA with LSR-ECD-Ig at 100 ug/dose 3 times/week for 10 days resulted in potent reduction of clinical score (FIG. 37A) and paw swelling (FIG. 37B) and histological damage (FIG. 37C). The efficacy of LSR-ECD-Ig (SEQ ID NO: 26) was similar to that obtained with CTLA4-Ig.

The efficacy of TMEM25-ECD-Ig, VSIG10-ECD-Ig and LY6G6F-ECD-Ig is evaluated in this CIA model.

Treatment with TMEM25-ECD-Ig (SEQ ID NO: 25) or with LSR-ECD-Ig (SEQ ID NO: 26) did not show efficacy in a more severe CIA model in which a boost with type II collagen emulsified in complete Freund's adjuvant is given on day 21. In this severe CIA Enbrel, a positive control, given at the same regimen and dosage, had very weak efficacy. Treatment with TMEM25-ECD-Ig also did not show a therapeutic effect in a CIA model with a collagen type II boost without the adjuvant given on day 21.

Study II: The Efficacy of LY6G6F ECD Ig Fusion Protein in the CIA Model was Studied Using a Modified CIA Model as Follows:

female DBA/1 mice (Taconic Farms, 9-11 weeks old) were acclimated for 7 days. On day 0, mice were immunized with chicken collagen/CFA, 0.05 mL EK-0210 emulsion/mouse (Hooke Laboratories, Inc.) and on day 20 a booster with chicken collagen/IFA, 0.05 mL EK-0211 emulsion/mouse (Hooke Laboratories, Inc.) was injected. Mice were scored daily and enrolled into one of the following treatment groups on the day of onset of arthritis:

Group 1: LY6G6F-ECD-Ig (SEQ ID NO: 23), i.p., Q2D, 30 mg/kg for 2 wks, 10 mL/kg.

Group 2: Vehicle (PBS) Q2D, for 2 wks, 10 mL/kg (negative control).

From the time of enrolment, mice were scored every other day for clinical signs and ankylosis according to the following scoring system:
Clinical score:

0	Normal paw.
1	One toe inflamed and swollen.
2	More than one toe, but not entire paw, inflamed and swollen, OR Mild swelling of entire paw.
3	Entire paw inflamed and swollen.
4	Very inflamed and swollen paw or ankylosed paw. If the paw is ankylosed, the mouse cannot grip the wire top of the cage.

Ankylosis score:

Paw Score	Clinical Observations
0	No ankylosis
1	Mild ankylosis
2	Moderate ankylosis
3	Severe ankylosis

The present Example shows that treatment of mice with established CIA with 30 mg/kg LY6G6F-ECD-Ig Q2D over 2 weeks from onset of arthritis resulted in alleviation of disease manifested in reduction of disease score (FIG. 38).

The efficacy of VSIG10-ECD-Ig (SEQ ID NO: 24) and TMEM25-ECD-Ig (SEQ ID NO: 25) is evaluated in a similar model.

Study III: Effect of LY6G6F, VSIG10, TMEM25 and LSR ECD-Ig Fusion Proteins on Tolerance Induction in Transfer Model of CIA

To further understand the effect of LY6G6F, VSIG10, TMEM25 and LSR ECD-Ig fusion proteins on immune regulation, the ability of these proteins to induce tolerance in a transfer model of arthritis is analysed.

In brief, spleen and LN cells from arthritic DBA/1 mice treated for 10 days with LY6G6F, VSIG10, TMEM25 and LSR ECD Ig fusion proteins (SEQ ID NOs: 23, 24, 25 and 26, respectively) or control Ig2a are removed and injected i.p into T-cell deficient C.B-17 SCID recipients. The mice then receive an injection of 100 µg type II collagen (without CFA), necessary for successful transfer of arthritis. Arthritis is then monitored in the SCID mice. Histology is performed and anti-collagen antibody levels are measured to determine that the LY6G6F, VSIG10, TMEM25 and LSR ECD Ig fusion proteins treatment confers long-term disease protection.

Example 38

Assessment of the Effect of LY6G6F, VSIG10, TMEM25 and LSR ECD-Ig Fusion Proteins in a Viral Infection Model of TMEV

Theiler's murine encephalomyelitis virus (TMEV) is a natural endemic pathogen of mice that causes an induced demyelinating disease (TMEV-IDD) in susceptible strains of mice (SJL/J, H-2KS) that resembles the primary progressive form of MS (Munz et al., Nat Rev Immunol 2009; 9:246-58). TMEV infection results in a life-long persistent virus infection of the CNS leading to development of a chronic T cell-mediated autoimmune demyelinating disease triggered via de novo activation of CD4 T cell responses to endogenous myelin epitopes in the inflamed CNS (i.e. epitope spreading) (Miller et al., Nat Med 1997; 3:1133-6; Katz-Levy et al., J Clin Invest 1999; 104:599-610).

SJL mice clear the majority of the virus within 21 days post infection, however a latent viral infection is maintained and infect microglia, astrocytes, and neurons. Disease symptoms are manifested around day 25-30 post infection.

5 The effect of treatment with LY6G6F, VSIG10, TMEM25 or LSR Ig fusion proteins (SEQ ID NOs: 23, 24, 25 and 26, respectively) on acute and chronic phases of viral infection is studied in the TMEV-IDD model by assessment of viral clearance and disease severity.

10 Method:

Female SJL/J mice (5-6 weeks) are infected with TMEV by intracranial inoculation in the right cerebral hemisphere of 3x10⁷ plaque forming units (PFU) of the BeAn strain 8386 of TMEV in 30 µl serum-free medium. From day 2 post infection mice are treated with Control Ig, LY6G6F, VSIG10, TMEM25 or LSR ECD-Ig fusion proteins, at 100 µg/dose each; 3 doses/week for 2 weeks.

Mice are followed for clinical scoring. On day 7 and day 14 post infection (after 3 and 6 treatments respectively) brains and spinal cords are collected from 5 mice in each treatment group for plaque assays. The tissues are weighted so that the ratio of PFU/mg of CNS tissue could be calculated after the plaque assay is completed.

TMEV Plaque Assay:

25 Brains and spinal cords of mice treated with Control Ig (mouse IgG2a), or with each of LY6G6F, VSIG10, TMEM25 or LSR ECD-Ig fusion proteins (SEQ ID NOs: 23, 24, 25 and 26, respectively) are collected at days 7 and 14 post-infection from non-perfused anesthetized mice. The Brains and spinal cords are weighed, and homogenized. CNS homogenates are serially diluted in DMEM and added to tissue culture-treated plates of confluent BHK-21 cells for 1 h incubation at room temperature, with periodic gentle rocking.

35 A media/agar solution is mixed 1:1 (volume:volume), added to cells and allowed to solidify at room temperature. The plates are then cultured at 34 deg C. for 5 days. At the end of culture, 1 ml of formalin is added and incubated at room temperature for 1 h to fix the BHK monolayer. The formalin is poured off into a waste container, and the agar is removed from the plates. Plaques are visualized by staining with crystal violet for 5 min, and plates are gently rinsed with diH2O. To determine PFU/ml homogenate, the number of plaques on each plate is multiplied by the dilution factor of the homogenate and divided by the amount of homogenate added per plate. The PFU/ml is divided by the weight of the tissue to calculate PFU/mg tissue.

Example 39

50 Assessment of the Effect of LY6G6F, VSIG10, TMEM25 and LSR ECD-Ig Fusion Proteins on Primary and Secondary Immune Response to Viral Infection in a Mouse Model of Influenza

55 To test the effect of LY6G6F, VSIG10, TMEM25 or LSR ECD-Ig fusion proteins (SEQ ID NOs: 23, 24, 25 and 26, respectively) on primary and secondary immune responses to viral infection, BALB/c naïve mice (for primary immune responses) and 'HA-memory mice', is used, as well as 'poly-clonal flu-memory mice' (to assess secondary responses mediated by memory CD4 T cells), which are generated as detailed in Teijaro et al., J Immunol. 2009: 182; 5430-5438, and described below.

65 To obtain 'HA-memory mice', first HA-specific memory CD4 T cells are generated, naïve CD4 T cells are purified from spleens of HA-TCR mice [BALB/c-HA mice which express transgenic T cell receptor (TCR) specific for influ-

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enza hemagglutinin (HA) peptide (110-119)] and primed in vitro by culture with 5.0 microg/ml HA peptide and mitomycin C-treated, T-depleted BALB/c splenocytes as APCs for 3 days at 37° C. The resultant activated HA-specific effector cells are transferred into congenic BALB/c (Thy1.1) hosts (5×10⁶ cells/mouse) to yield “HA-memory mice” with a stable population of HA-specific memory CD4 T cells.

To obtain ‘polyclonal-memory mice’, first polyclonal influenza-specific memory CD4 T cells are generated, by infecting BALB/c mice intranasally with a sublethal dose of PR8 influenza, CD4 T cells are isolated 2-4 months postinfection, and the frequency of influenza-specific memory CD4 T cells is determined by ELISPOT. CD4 T cells from previously primed mice are transferred into BALB/c hosts to generate “polyclonal flu-memory” mice with a full complement of endogenous T cells.

Primary and secondary responses to influenza virus are tested by infecting naïve BALB/c mice or BALB/c-HA memory mice and BALB/c ‘polyclonal flu-memory mice’ with sublethal or lethal doses of PR8 influenza virus by intranasal administration.

Mice are treated with LY6G6F, VSIG10, TMEM25 or LSR ECD-Ig fusion proteins or with mIgG2a control before and following influenza challenge. Weight loss and mortality will be monitored daily. Six days after the challenge, viral content in the bronchoalveolar lavage (BAL) is analyzed by collecting lavage liquid and testing the supernatant for viral content by determining the tissue culture infectious dose 50% (TCID50) in MDCK cells. In addition, lung tissue histopathology is performed.

To test the effect LY6G6F, VSIG10, TMEM25 and LSR ECD-Ig fusion proteins on T cell expansion BALB/c or BALB/c-HA memory mice or BALB/c ‘polyclonal flu-memory mice’ are infected as above and administered with BrdU (1 mg/dose) on days 3, 4 and 5 post infection. On day 6, spleen and lung are harvested and BrdU incorporation is estimated. Cytokine production by lung memory CD4 T cells during influenza challenge is also studied in HA-specific memory CD4 T cells stimulated in vitro with HA peptide in the presence LY6G6F, VSIG10, TMEM25 or LSR ECD-Ig fusion proteins or with IgG2a for 18 hours.

Example 40

Assessment of the Effect of LY6G6F, VSIG10, TMEM25 and LSR ECD—Ig Fusion Proteins on Primary and Secondary Cd8 T Cell Response to Viral Infection in a Mouse Model of Influenza

The effect of LY6G6F, VSIG10, TMEM25 and LSR ECD Ig fusion proteins (SEQ ID NOs: 23, 24, 25 and 26, respectively) on primary CD8 T cell responses to influenza virus is studied according to methods as described in the literature (Hendriks et al., J Immunol 2005; 175; 1665-1676; Bertram et al., J Immunol. 2004; 172:981-8) using C57BL/6 mice infected with influenza A HKx31 by intranasal or intraperitoneal administration. LY6G6F, VSIG10, TMEM25 or LSR ECD Ig fusion proteins or mIgG2a control are administered during priming. Animal weight loss and mortality is monitored daily. To follow virus-specific CD8+ T cells, MHC H-2 Db tetramers loaded with the major CD8 T cell epitope, the NP₃₆₆₋₃₇₄ peptide are used. Virus-specific H-2D^b/NP₃₆₆₋₃₇₄ CD8+ T cells in the lung, draining lymph nodes, and spleen are expected to reach a peak around day 8-10 post infection and decline thereafter to only 1.5% virus-specific

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CD8 T cells (Hendriks et al J Immunol 2005; 175; 1665-1676; Bertram et al., J Immunol. 2002; 168:3777-85; Bertram et al., J Immunol. 2004; 172:981-8). Thus, mice are sacrificed at days 8 and 21 post infection, and virus-specific CD8 T cell numbers is evaluated in the lung, draining lymph nodes and spleen. Viral clearance is assessed. CD8 T cell responses are evaluated in spleen cell suspensions, and include intracellular IFN-γ staining and CTL activity, as previously described (Bertram et al., J Immunol. 2004; 172:981-8) and detailed below.

Cells are surface-stained with FITC-conjugated anti-mouse CD62L, PE-conjugated anti-mouse CD8 to measure CD8+ activated T cells (or anti-mouse CD4 to follow CD4+ cells). In addition to these Abs, allophycocyanin-labeled tetramers consisting of murine class I MHC molecule H-2D^b, β₂-microglobulin, and influenza NP peptide, NP₃₆₆₋₃₇₄ are used to measure influenza-specific CD8 T cells. For intracellular IFN-γ staining, cell suspensions are restimulated in culture medium for 6 h at 37° C. with 1 μM NP₃₆₆₋₃₇₄ peptide and GolgiStop (BD PharMingen, San Diego, Calif.). Cells are then harvested, resuspended in PBS/2% FCS/azide, and surface stained with PE-anti-CD8 and FITC-anti-CD62L as described above. After surface staining, cells will be fixed in Cytofix/Cytoperm solution (BD PharMingen) and then stained with allophycocyanin-conjugated antimouse IFN-γ diluted in 1× perm/wash solution (BD PharMingen). Samples are analyzed by Flow Cytometry.

For cytotoxicity assays (CTL responses) splenocytes from influenza-infected mice are incubated for 2 h at 37° C. to remove adherent cells. Serial 3-fold dilutions of effectors are assayed for anti-influenza NP₃₆₆₋₃₇₄-specific CTL activity against ⁵¹Cr-labeled EL4 cells pulsed with 50 μM NP₃₆₆₋₃₇₄ peptide for 6 h as described by Bertram et al 2002 and Bertram et al 2004.

At 3 weeks postinfection, some mice are rechallenged with the serologically distinct influenza A/PR8/34 (PR8), which shares the NP gene with influenza A HKx31, but differs in hemagglutinin and neuraminidase, so that neutralizing Abs do not limit the secondary CTL response. Mice are sacrificed at days 5 & 7 following virus rechallenge, and virus-specific CD8 T cell numbers is evaluated in the lung, draining lymph nodes and spleen as described by Hendriks et al and Bertram et al (Hendriks et al., J Immunol 2005; 175; 1665-1676; Bertram et al., J Immunol. 2004; 172:981-8) and detailed above. Secondary CD8 T cell responses, including intracellular IFN-γ staining and CTL activity, are evaluated in spleen cell suspensions of mice at days 5 & 7 following virus rechallenge, as described above.

To determine the effect of LY6G6F, VSIG10, TMEM25 and LSR ECD-Ig fusion proteins on expansion and accumulation of memory CD8+ T cells during the secondary response, adoptive transfer experiments are performed, according to methods previously described (Hendriks et al., J Immunol 2005; 175; 1665-1676; Bertram et al., J Immunol. 2004; 172:981-8): mice are immunized with influenza A HKx31. Twenty-one days later, T cells are purified from spleens on mouse T cell enrichment immunocolumns (Cedarlane Laboratories, Hornsby, Ontario, Canada) and labeled with CFSE (alternatively Thy1.1 congenic mice are used as recipients). Equal numbers of tetramer-positive T cells are injected through the tail vein of recipient mice. Mice are rechallenged with influenza virus as described above, and 7 days later splenocytes are evaluated for donor virus-specific CD8 T cells, as detailed above.

Assessment of Protein Expression in Exhausted T Cells, and the Binding and Effect of the LY6G6F, VSIG10, TMEM25 and LSR ECD-Ig Fusion Proteins on Reversing Exhausted T Cell Phenotype

Memory CD8 T-cell differentiation proceeds along distinct pathways after an acute versus a chronic viral infection (Kleerman and Hill Nat Immunol 6, 873-879, 2005). Memory CD8 T cells generated after an acute viral infection are highly functional and constitute an important component of protective immunity. In contrast, chronic infections are often characterized by varying degrees of functional impairment of virus-specific T-cell responses, and this defect is a principal reason for the inability of the host to eliminate the persisting pathogen. Although functional effector T cells are initially generated during the early stages of infection, they gradually lose function during the course of the chronic infection leading to exhausted phenotype characterized by impaired T cell functionality.

Study I. The Effect of LY6G6F, VSIG10, TMEM25 and LSR ECD Ig Fusion Proteins on Clearance of Viral Infection and on T Cell Functions During Acute and Chronic Viral Infection.

The effect of LY6G6F, VSIG10, TMEM25 and LSR ECD Ig fusion proteins (SEQ ID NOs: 23, 24, 25 and 26, respectively) on acute and chronic viral infection is evaluated in a mouse model of infection with LCMV (lymphocytic choriomeningitis virus) according to methodology described by Wherry et al J. Virol. 77: 4911-4927, 2003 and Barber et al Nature, 2006, and detailed below.

Two LCMV strains that can cause either acute or chronic infections in adult mice are used; the Armstrong strain which is cleared within a week, and the clone 13 strain which establishes a persistent infection that can last for months. As these two strains differ in only two amino acids, preserving all known T cell epitopes, it is possible to track the same CD8 T cell responses after an acute or chronic viral infection. In contrast to the highly robust memory CD8 T cells generated after an acute Armstrong infection, LCMV-specific CD8 T cells become exhausted during a persistent clone 13 infection (Wherry et al J. Virol. 77: 4911-4927, 2003; Barber et al., Nature. 2006; 439:682-7).

Mice are infected with 2×10^5 PFU of Armstrong strain of LCMV intraperitoneally to initiate acute infection or 2×10^6 PFU of Cl-13 intravenously to initiate chronic infection. Mice are treated i.p. with LY6G6F, VSIG10, TMEM25 or LSR ECD Ig fusion proteins or with mIgG2a control, and with specific anti-LY6G6F, anti-VSIG10, anti-TMEM25, anti LSR—antibody or an isotype control.

The mice are monitored for numbers of virus specific CD8 T cells in the spleen, using virus-specific MHC tetramer epitopes, such as D^bNP₃₉₆₋₄₀₄ and D^bGP₃₃₋₄₁ which differ in acute or chronic infections. CD8 T cell functional assays, such as intracellular cytokines levels and CTL activity, are carried out as described by Wherry et al J. Virol. 77: 4911-4927, 2003, and similarly to those described in Example 40. Additional assays include production by splenocytes after stimulation with virus specific epitopes; and assessment of viral titers in the serum and in the spleen, liver, lung and kidney (Wherry et al J. Virol. 77: 4911-4927, 2003; Barber et al., Nature. 2006; 439:682-7).

Study II.

Assessment of LY6G6F, VSIG10, TMEM25 and LSR expression on exhausted T cells and binding of LY6G6F, VSIG10, TMEM25 and LSR ECD Ig fusion proteins to

exhausted T cells in order to evaluate regulation of these proteins or their counterpart receptors during exhaustion of T cells:

T cells are isolated from mice with chronic LCMV infection induced with Cl-13 strain. The cells are co-stained with fluorescently labeled anti-PD-1 Ab as positive control (PD-1 is highly expressed by exhausted T cells) and biotinylated LY6G6F, VSIG10, TMEM25 and LSR ECD Ig fusion proteins or biotinylated anti-LY6G6F, anti-VSIG10, anti-TMEM25 and anti-LSR fusion proteins antibodies, and respective isotype control. Binding is detected by FACS analysis using fluorescently labeled streptavidin.

Example 42

Assessment of LY6G6f, VSIG10, TMEM25 and/or LSR Protein Expression In Follicular Helper T (Tfh) Cells and the Binding of Ig Fusion Proteins to Tfh Cells

Follicular helper T (Tfh) cells are a subset of CD4+ T cells specialized in B cell help (reviewed by Crotty, Annu. Rev. Immunol. 29: 621-663, 2011). Tfh cells migrate into B cell follicles within lymph nodes, and interact with cognate B cells at the T cell-B cell border and subsequently induce germinal center B cell differentiation and germinal center formation within the follicle (Reviewed by Crotty, Annu. Rev. Immunol. 29: 621-663, 2011). The requirement of Tfh cells for B cell help and T cell-dependent antibody responses, indicates that this cell type is of great importance for protective immunity against various types of infectious agents, as well as for rational vaccine design.

Tfh cells are readily identifiable at the peak of the CD4+ T cell response to an acute lymphocytic choriomeningitis virus (LCMV) infection as CXCR5^{hi}SLAMF6^{lo}BTLA^{hi}PD1^{hi}Bcl6⁺ virus-specific CD4+ T cells (Choi et al 2011, Immunity 34: 932-946). T cells are isolated from mice with acute LCMV infection induced with 2×10^5 PFU of Armstrong strain of LCMV administered intraperitoneally. The cells are co-stained with fluorescently labeled antibodies for markers of Tfh (CXCR5, PD1, BTLA, Bcl6) which are highly expressed by Tfh cells, and biotinylated LY6G6F, VSIG10, TMEM25 and LSR ECD-Ig fusion proteins or biotinylated antibodies specific for LY6G6F, VSIG10, TMEM25 and LSR, and respective isotype controls. Binding of Fc fused protein or antibody is detected by FACS analysis using fluorescently labeled streptavidin.

Example 43

Assessment of the Effect of LY6G6f, VSIG10, TMEM25 and LSR Ig Fusion Proteins on Follicular Helper T (Tfh) Cells Generation and Activity

In order to investigate the effect of LY6G6F, VSIG10, TMEM25 and LSR ECD Ig fusion proteins on Tfh differentiation and development of B cell immunity in vivo, C57BL/6 are treated with LY6G6F, VSIG10, TMEM25 and LSR ECD Ig fusion proteins and an isotype control throughout the course of an acute viral infection with Armstrong strain of LCMV (lymphocytic choriomeningitis virus). Tfh differentiation and Bcl6 protein expression is assessed by FACS analysis as described by Eto et al 2011 (PLoS One 6: e17739). Splenocytes are analyzed 8 days following LCMV infection, Tfh generation (CD44^{hi}CXCR5^{hi}SLAMF6^{lo}) and Bcl6 expression is evaluated by FACS analysis. In addition, the effect of LY6G6F, VSIG10, TMEM25 and LSR ECD Ig fusion pro-

teins (SEQ ID NOs: 23, 24, 25 and 26, respectively) on antigen-specific B cell responses is evaluated as described by Eto et al 2011 (PLoS One 6: e17739), including titers of anti-LCMV IgG in the serum at 8 days following LCMV infection, and quantitation by FACS analysis of plasma cell (CD138⁺IgD⁺) development at 8 days post-infection, gated on CD19⁺ splenocytes.

Example 44

The Effect of LY6G6f, VSIG10, TMEM25 and LSR ECD Ig Fusion Proteins In Modulation of Type 1 Diabetes in Nod Mice, Cd28-KO Nod, and B7-2-KO NOD

The effect of LY6G6F, VSIG10, TMEM25 and LSR ECD Ig fusion proteins are studied in a widely used mouse model of type 1 diabetes: nonobese diabetic (NOD) mice which develop spontaneous In NOD mice, spontaneous insulinitis, the hallmark pathologic lesion, evolves through several characteristic stages that begin with peri-insulinitis and end with invading and destructive insulinitis and overt diabetes. Peri-insulinitis is first observed at 3-4 wk of age, invading insulinitis at 8-10 wk, and destructive insulinitis appears just before the onset of clinical diabetes, with the earliest cases at 10-12 wk. At 20 wk of age, 70-80% of female NOD mice become diabetic (Ansari et al 2003 J. Exp. Med. 198: 63-69).

Two KO mice: CD-28-KO NOD mice and B7-1/B7-2 double KO NOD mice, —which develop accelerated diabetes (Lenschow et al 1996 Immunity 5: 285-293; Salomon et al 2000 Immunity 12: 431-440), are also used.

Study I:

NOD mice are treated with LY6G6F, VSIG10, TMEM25 or LSR ECD-Ig fusion proteins (SEQ ID NOs: 23, 24, 25 and 26, respectively) early and late phases during the evolution of diabetes, before or after disease onset, to examine the effects of these compounds on disease pathogenesis and to demonstrate that such treatment reduces disease onset and ameliorates pathogenesis. To study the effect on insulinitis, blood glucose levels are measured 3 times/week, for up to 25 weeks (Ansari et al 2003 J. Exp. Med. 198: 63-69).

Mechanism of disease modification and mode of action is studied by experimental evaluation of individual immune cell types: pancreas, pancreatic LNs and spleen will be harvested to obtain Tregs, Th subtypes and CD8 T cells, DCs and B cells. Effect on cytokines secretion from cells isolated from pancreas, pancreatic LN and spleen is analysed, focused on IFN γ , IL-17, IL-4, IL-10 and TGF β . Upon effect of the tested compounds, the mechanism of disease modification is studied by examination of individual immune cell types (including Tregs, Th subtypes and CD8 T cells, DCs and B cells); cytokines (IFN γ , IL-17, IL-4, IL-10 and TGF β) and histology. Histological analysis of the pancreas is carried out to compare the onset of insulinitis, and the lymphocyte infiltration.

Study II—the effect of LY6G6F Ig Fusion Proteins in Modulation of Type 1 Diabetes in Adoptive Transfer Model

To further investigate the mode of action of the Ig fusion proteins, an adoptive transfer model of diabetes is used. T cells from diabetic or prediabetic NOD donors are transferred to NOD SCID recipient mice. These mice are monitored for development of diabetes. The urine glucose and blood glucose, and assess histology of the pancreas, and T cell responses are monitored as described in the previous example.

Study III:

Diabetes is also Induced by the transfer of activated CD4⁺CD62L⁺CD25⁺BDC2.5 T cells (transgenic for TCR recognizing islet specific peptide 1040-p31 activated by incubation with 1040-p31) to NOD recipients. Mice are treated with LY6G6F, VSIG10, TMEM25 or LSR ECD Ig fusion proteins, control mIgG2a or positive control. Treatments begin 1 day following transfer. Mice are followed for glucose levels 10-28 days post transfer (Bour-Jordan et al., J Clin Invest. 2004; 114(7):979-87).

Seven days post treatment pancreas, spleen, pancreatic LN and peripheral lymph node cells are extracted and examined for different immune cell populations. In addition, recall responses are measured by testing ex-vivo proliferation and cytokine secretion in response to p31 peptide.

LY6G6F, VSIG10, TMEM25 and LSR ECD Ig fusion proteins prevent or reduce disease onset or the severity thereof in the above studies.

Example 45

The Effect of LY6G6f, VSIG10, TMEM25 and LSR ECD Ig Fusion Proteins in Lupus Mouse Models

Study I:

The lupus-prone mouse model, (NZB \times NZW)F1 (B/W) is used. Cyclophosphamide (CTX) is the primary drug used for diffuse proliferative glomerulonephritis in patients with renal lupus. Daikh and Wofsy reported that combination treatment with CTX and CTLA4-Ig was more effective than either agent alone in reducing renal disease and prolonging survival of NZB/NZW F1 lupus mice with advanced nephritis (Daikh and Wofsy, J Immunol, 166(5):2913-6 (2001)). In the proof-of-concept study, treatments with LY6G6F, VSIG10, TMEM25 or LSR ECD Ig fusion proteins and CTX either alone or in combination are tested.

Blood samples are collected 3 days before the protein treatment and then every other week during and after treatments for plasma anti-dsDNA autoantibody analysis by ELISA. Glomerulonephritis is evaluated by histological analysis of kidneys. Proteinuria is measured by testing fresh urine samples using urinalysis dipsticks.

LY6G6F, VSIG10, TMEM25 and LSR ECD Ig fusion proteins (SEQ ID NOs: 23, 24, 25 and 26, respectively) have a beneficial effect in at least ameliorating lupus nephritis.

Study II:

The NZM2410-derived B6.Sle1.Sle2.Sle3 mouse model of SLE is used. NZM2410 is a recombinant inbred strain produced from NZB and NZW that develops a highly penetrant lupus-like disease with an earlier onset of disease (Blenman et al 2006 Lab. Invest. 86: 1136-1148). The effect of LY6G6F, VSIG10, TMEM25 and LSR ECD Ig fusion proteins is studied in this model by assessment of proteinuria and autoantibodies as described above.

Study III:

An induced lupus model is used. This model is based on chronic graft-vs-host (cGVH) disease induced by the transfer of Ia-incompatible spleen cells from one normal mouse strain (such as B6.C-H2(bm12)/KhEg (bm12)) to another (such as C57BL/6), which causes an autoimmune syndrome resembling systemic lupus erythematosus (SLE), including anti-double-stranded DNA (anti-dsDNA) autoantibodies and immune complex-type proliferative glomerulonephritis (Appleby et al Clin. Exp. Immunol. 1989 78: 449-453); Eisenberg and Choudhury 2004 Methods Mol. Med. 102: 273-284).

Lupus is induced in this model following injection of spleen cells from bm12 mice into C57BL/6 recipients. The

effect of LY6G6F, VSIG10, TMEM25 and LSR ECD Ig fusion proteins is studied in this model by assessment of proteinuria and autoantibodies as described above. T cell and responses B cell responses will also be evaluated.

Study IV:

The MRL/lpr lupus prone mouse model is used. The effect of LY6G6F, VSIG10, TMEM25 and LSR ECD Ig fusion proteins is studied in this model by assessment of proteinuria and autoantibodies as described above.

Example 46

The Effect of LY6G6f, VSIG10, TMEM25 and LSR ECD Ig Fusion Proteins in the Control of Intestinal Inflammation

An adoptive transfer mouse model of colitis in mice is used, whereby Transfer of CD45RB^{high}-CD4⁺ naïve T cells from BALB/c mice to syngeneic SCID mice leads to the development of an IBD-like syndrome by 6-10 wks after T cell reconstitution, similar to human Crohn's disease.

SCID mice are reconstituted by i.p. injection of syngeneic CD45RB^{high}-CD4⁺ T cells either alone or cotransferred with syngeneic CD45RB^{low}-CD4⁺ or CD25⁺CD4⁺ cells (4×10⁵/mouse of each cell population) (Liu et al., J Immunol. 2001; 167(3): 1830-8). Colitic SCID mice, reconstituted with syngeneic CD45RB^{high}CD4⁺ T cells from spleen of normal mice, are treated i.p. with LY6G6F, VSIG10, TMEM25 or LSR ECD Ig fusion proteins or Ig isotype control, twice a week starting at the beginning of T cell transfer up to 8 wk. All mice are monitored weekly for weight, soft stool or diarrhea, and rectal prolapse. All mice are sacrificed 8 wk after T cell transfer or when they exhibit a loss of 20% of original body weight. Colonic tissues are collected for histologic and cytologic examinations. LY6G6F, VSIG10, TMEM25 and LSR ECD Ig fusion proteins have a beneficial effect in at least ameliorating inflammatory bowel disease.

Example 47

The Effect of LY6G6F, VSIG10, TMEM25 and LSR ECD Ig Fusion Proteins in Mouse Model of Psoriasis

Study I: Establishment of Psoriasis SCID Xenograft Model.

Human psoriasis plaques are transplanted on to the SCID mice. Shave biopsies (2.5_2.5 cm) are taken from patients with generalized plaque psoriasis involving 5-10% of the total skin that did not receive any systemic treatment for psoriasis or phototherapy for 6 months and did not receive any topical preparations other than emollients for 6 weeks. The biopsies are obtained from active plaques located on the thigh or arm. Each piece of biopsy is divided into four equal parts of approximately 1 cm² size. Each piece is transplanted to a separate mouse.

Under general anesthesia, a graft bed of approximately 1 cm² is created on the shaved area of the back of a 7- to 8-week-old CB 17 SCID mouse by removing a full-thickness skin sample, keeping the vessel plexus intact on the fascia covering the underlying back muscles. The partial thickness human skin obtained by shave biopsy is then orthotopically transferred onto the graft bed. Nexaband, a liquid veterinary bandage (Veterinary Products Laboratories, Phoenix, Ariz.) is used to attach the human skin to the mouse skin and an antibiotic ointment (bacitracin) is applied. Mice are treated intraperitoneally three times per week for 4 weeks with LY6G6F, VSIG10, TMEM25 or LSR ECD Ig fusion proteins, isotype control or CTLA4-Ig (positive control).

Punch biopsies (2 mm) are obtained on day 0 (before treatment) and day 28 (after treatment) of the study period. Biopsies are snap frozen and cryosections for histopathological and immunohistochemical studies. Therapeutic efficacy is determined by comparing pre- and post treatment data: (i) rete peg lengths to determine the effect on epidermal thickness and (ii) the level of lymphomononuclear cell infiltrates to determine the effect on inflammatory cellular infiltrates. (Raychaudhuri et al. 2008, J Invest Dermatol.;128(8):1969-76; Boehncke et al., 1999 Arch Dermatol Res 291:104-6).

LY6G6F, VSIG10, TMEM25 and LSR ECD Ig fusion proteins (SEQ ID NOs: 23, 24, 25 and 26, respectively) have a beneficial effect in at least ameliorating psoriasis.

Study II: The Effect of LY6G6f, VSIG10, TMEM25 and LSR Cd45RBhi Cd4+ T Cells in SCID Mice

Immunocompromised mice are injected intravenously (i.v.) with 0.3_10⁶ CD4⁺ CD45RBhi cells. On the day following the adoptive transfer of cells, mice are injected intraperitoneally (i.p.) with 10 microg of staphylococcal enterotoxin B (Davenport et al., Int Immunopharmacol. 2002 April; 2(5):653-72). Recipient mice are treated with LY6G6F, VSIG10, TMEM25 or LSR ECD-Ig fusion proteins (SEQ ID NOs: 23, 24, 25 and 26, respectively), isotype control or CTLA4-Ig (positive control). Mice are evaluated once a week for 8 weeks for weight loss and presence of skin lesions.

Obtained results are similar to those described above.

Example 48

The Effect of LY6G6f, VSIG10, TMEM25 and LSR ECD Ig Fusion Proteins in Modulating Transplant Rejection

Study I: The Effect of LY6G6F, VSIG10, TMEM25 and LSR in a Model of Allogeneic Islet Transplantation in Diabetic Mice.

To test the effect of LY6G6F, VSIG10, TMEM25 and LSR ECD Ig fusion proteins (SEQ ID NOs: 23, 24, 25 and 26, respectively) on transplant rejection, a model of allogeneic islet transplantation is used. Diabetes is induced in C57BL/6 mice by treatment with streptozotocin. Seven days later, the mice are transplanted under the kidney capsule with pancreatic islets which are isolated from BALB/c donor mice. Recipient mice are treated with LY6G6F, VSIG10, TMEM25 or LSR ECD Ig fusion proteins or with mIgG2a as a negative control. Tolerance with ECDI-fixed donor splenocytes is used as the positive control for successful modulation islet graft rejection. Recipient mice are monitored for blood glucose levels as a measure of graft acceptance/rejection (Luo et al., PNAS, Sep. 23, 2008_vol. 105_no. 38_14527-14532).

Study II: The Effect of LY6G6f, VSIG10, TMEM25 and LSR in the Hya-Model of Skin Graft Rejection.

In humans and certain strains of laboratory mice, male tissue is recognized as non-self and destroyed by the female immune system via recognition of histocompatibility-Y chromosome encoded antigens (Hya). Male tissue destruction is thought to be accomplished by cytotoxic T lymphocytes in a helper-dependent manner.

To test the effect of LY6G6F, VSIG10, TMEM25 and LSR ECD Ig fused proteins (SEQ ID NOs: 23, 24, 25 and 26, respectively) on transplanatation, the Hya model system is used, in which female C57BL/6 mice receive tail skin grafts from male C57BL/6 donors.

In this study, female C57BL/6 mice are engrafted with orthotopic split-thickness tail skin from age matched male C57BL/6 mice. The mice are treated with LY6G6F, VSIG10,

TMEM25 or LSR ECD Ig fusion proteins, isotype control mIgG2a. Immunodominant Hya-encoded CD4 epitope (Dby) attached to female splenic leukocytes (Dby-SP) serve as positive control for successful modulation of graft rejection (Martin et al., J Immunol. 2010 Sep. 15; 185(6): 3326-3336). Skin grafts are scored daily for edema, pigment loss and hair loss. Rejection is defined as complete hair loss and more than 80% pigment loss.

In addition, T cell recall responses of cells isolated from spleens and draining lymph nodes at different time points are studied in response to CD4 specific epitope (Dby), CD8 epitopes (Uty and Smcy) or irrelevant peptide (OVA 323-339) while anti CD3 stimulation is used as positive control for proliferation and cytokine secretion.

Study III:

The effect of LY6G6F, VSIG10, TMEM25 and LSR ECD Ig fusion proteins on graft rejection is studied in a murine model of syngeneic bone marrow cells transplantation using the Hya model system described above. Male hematopoietic cells expressing the CD45.1 marker are transplanted to female host mice which express the CD45.2 congenic marker. Female hosts are treated with LY6G6F, VSIG10, TMEM25 or LSR ECD Ig fusion proteins or with isotype control mIgG2a. The female hosts are followed over time and the presence of CD45.1+ cells is monitored.

Example 49

Establishment of the Role of LY6G6F, VSIG10, TMEM25 and/or LSR Proteins According to at Least Some Embodiments of the Invention as Modulators of Cancer Immune Surveillance

1) In Vivo Proof of Concept

a) Mouse Cancer Syngeneic Model:

(i) Tumor cells, over expressing any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins or a non-relevant control protein are transplanted to genetically matched mice. Tumor volume (and tumor weight after sacrificing the animals) and ex vivo analysis of immune cells from tumor draining lymph nodes or spleens are then examined to demonstrate the rejection of the tumor to be delayed (i.e. tumor over expressing LY6G6F, VSIG10, TMEM25 and/or LSR grow faster than tumors over expressing the non-relevant control protein). Ex vivo analysis of immune cells from tumor draining lymph nodes is expected to reveal an increase in the frequency of regulatory T cells and a decrease in the responsiveness of effector T cells to stimulation. (J. Exp. Med. 2011 Vol. 208 No. 3 577-592).

(ii) In vivo syngeneic model using the extra cellular domain of the mouse orthologs of any one of LY6G6F, VSIG10, TMEM25 and/or LSR protein fused to an antibody Fc fragment (mouse ECD-Fc) (SEQ ID NO: 23, 24, 25 and 26, respectively) is tested as follows. The mouse ECD-FC is injected IV to C57BL/6 mice at 3-4 day intervals, after tumor establishment, as described in J Immunol 2010; 185; 2747-2753. Tumor volume (and tumor weight after sacrificing the animals) and ex vivo analysis of immune cells from tumor draining lymph nodes or spleens are then examined. As a result of IV treatment with Mouse ECD-FC of LY6G6F, VSIG10, TMEM25 and/or LSR the rejection of the tumor is delayed (i.e. in mice treated with the Mouse ECD-FC of LY6G6F, VSIG10, TMEM25 and/or LSR tumors grow faster than tumors in mice treated with non-relevant control protein). Ex vivo analysis of immune cells from tumor draining

lymph nodes reveal an increase in the frequency of regulatory T cells and a decrease in the responsiveness of effector T cells to stimulation.

(iii) Establishment of a syngeneic tumor and treat with neutralizing antibodies directed against any one of LY6G6F, VSIG10, TMEM25 and/or LSR protein (1, 3, 5, 7, 11, 143, 13, 15-17, 18, 28, 29-32). Tumor cells are transplanted to genetically identical mice. After the establishment of tumors, mice are injected IV with different doses of neutralizing antibodies aimed against any one of LY6G6F, VSIG10, TMEM25 and/or LSR protein. As a result of IV treatment with neutralizing antibodies specific for any one of LY6G6F, VSIG10, TMEM25 and/or LSR protein the rejection of the tumor is increased (i.e. in mice treated with neutralizing antibodies against any one of LY6G6F, VSIG10, TMEM25 and/or LSR protein tumors grow slower than tumors in mice treated with non-relevant antibody). Ex vivo analysis of immune cells from tumor draining lymph nodes reveal a decrease in the frequency of regulatory T cells and an increase in the responsiveness of effector T cells to stimulation.

b) Human Cancer Xenograft Model:

(i) Reconstitution of the tumor immune response in a model of immune compromised NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ mice (Jackson lab), "NSG" mice. Human tumor is established in NSG model, and APCs pre-loaded with Tumor antigens, or/and T cells (CD8 T cells pre-activated with cancer target cells are transferred into tumor bearing NSG mice (all cells transplanted/injected originate from cancer patients). This model consists of four arms: 1. APC's over expressing any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins, 2. silencing of any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins (either siRNA or ShRNA) on APC's, 3. Cancer cells over expressing any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins and 4. Silencing of any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins (either siRNA or ShRNA) on cancer cells. Positive (e.g. B7-H1, PD-L1) and negative (e.g. Vector and cells alone) controls are included. Tumor volume or tumor metastasis and mouse survival are then examined (J. Exp. Med.; 2006; Vol. 203; p. 871-881). Over expression of any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins either on APC's or on Tumor cells, lead to delayed rejection of the tumor (i.e. in mice treated with the APC's or tumor cells over expressing any of LY6G6F, VSIG10, TMEM25 and/or LSR tumors grow faster than tumors in mice treated with non-relevant control protein). Silencing (with SiRNA or SHRNA) of any of LY6G6F, VSIG10, TMEM25 and/or LSR either on APC's or on tumor cells lead to enhanced rejection of the tumor.

(ii) Establishment of the NSG cancer Xenograft as described above (without genetic manipulation of APC's and/or cancer cells) and treatment with neutralizing antibodies directed against the any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins. Treatment of the NSG Xenograft model with neutralizing antibodies directed against any of LY6G6F, VSIG10, TMEM25 and/or LSR is gives rise to enhanced rejection of the tumor.

2) In Vitro Validation of Natural Killer (NK) Cell Activity

a) Binding Assay:

(i) Binding assay with human LY6G6F, VSIG10, TMEM25 and/or LSR ECD-FC proteins on activated primary-culture NK cells is performed as described in J Immunol 2005; 174; 6692-6701. If the counter receptor of LY6G6F, VSIG10, TMEM25 and/or LSR is expressed on NK cells, binding of LY6G6F, VSIG10, TMEM25 and/or LSR ECD-FC is observed.

(ii) Binding assay with a specific antibody directed against the any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins on activated primary-culture NK cells is performed as described in PNAS, 2009, vol. 109; 17858-17863. If any one of LY6G6F, VSIG10, TMEM25 and/or LSR is expressed on NK cells, binding of LY6G6F, VSIG10, TMEM25 and/or LSR specific antibody, respectively, is observed.

(iii) Binding assay with human LY6G6F, VSIG10, TMEM25 and/or LSR ECD-FC proteins on various human cancer cell lines that may serve as target cells for NK killing is performed as described in J Immunol 2006; 176; 6762-6769. If the counter receptor of any one of LY6G6F, VSIG10, TMEM25 and/or LSR is expressed on the cancer target cells, binding of LY6G6F, VSIG10, TMEM25 and/or LSR ECD-Fc, respectively is observed.

b) Functional Killing Assay:

(i) Killing assays are performed using an over expression system (either NK cells or cancer target cells, over expressing any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins). The NK cells (effector; e) are co-incubated with radioactive (S35) labeled cancer target cells (target; t) in various e: t ratios, as described in PNAS, 2009, vol. 109; 17858-17863. Lysis of target cells by NK killing activity is then evaluated by measurement of radioactive emission. Over expression of any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins on the target cancer cells and/or the NK cell lines lead to down regulation of the NK mediated killing activity.

(ii) Killing assays are performed in the presence of the human LY6G6F, VSIG10, TMEM25 and/or LSR ECD-FC proteins, as described in PLoS ONE; 2010; Vol. 5; p. 1-10. Treatment with the ECD-Fc of any of LY6G6F, VSIG10, TMEM25 and/or LSR interfere with the interaction of LY6G6F, VSIG10, TMEM25 and/or LSR with their counter receptors and thus decrease their inhibitory activity, giving rise to enhanced killing activity.

(iii) Killing assays are performed in the presence of a neutralizing antibody directed against any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins, as described in PNAS, 2009, vol. 109; 17858-17863. Treatment with neutralizing antibodies directed towards any of LY6G6F, VSIG10, TMEM25 and/or LSR, give rise to enhanced NK killing activity.

(iv) "Re-directed killing assay" is performed as follows: cancer target cells expressing high density Fc receptors are coated with activating antibodies directed against any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins and exposed to NK cells (expressing the designated LY6G6F, VSIG10, TMEM25 and/or LSR protein), as described in PNAS, 2009, vol. 109; 17858-17863. Cross linking of any one of LY6G6F, VSIG10, TMEM25 and/or LSR with activating antibodies give rise to reduced NK mediated killing activity.

3) Expression Analysis

a) Expression of LY6G6F, VSIG10, TMEM25 and/or LSR Proteins on Cells Isolated from Human Tumor Biopsies

i) Expression validation of any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins using specific antibodies directed against the any one of LY6G6F, VSIG10, TMEM25 and/or LSR proteins, respectively, is carried out on separated cell populations from the tumor. Various cell populations are freshly isolated from tumor biopsies (e.g. Tumor cells, endothelial, tumor associated macrophages (TAMs) and DCs, B cells and different T cells (CD4, CD8 and Tregs) as described in J. Exp. Med.; 2006; Vol. 203; p. 871-881 and Cancer res. 2007; 67; 8900-8905, to demonstrate expression of any of LY6G6F, VSIG10, TMEM25 and/or LSR in tumor cells and on tumor stroma and immune infiltrate.

ii) Binding assay is performed with the human LY6G6F, VSIG10, TMEM25 and/or LSR ECD-FC proteins on separated cell populations from the tumor. Isolate various cell populations from tumor biopsies (e.g. Tumor cells, endothelial, tumor associated macrophages (TAMs) and DCs, B cells and different T cells (CD4, CD8 and Tregs) freshly isolated from tumors as described in J. Exp. Med.; 2006; Vol. 203; p. 871-881 and Cancer res. 2007; 67; 8900-8905, to show expression of the counter receptor for any of LY6G6F, VSIG10, TMEM25 and/or LSR in tumor cells and on tumor stroma and immune cells.

b) Expression of LY6G6F, VSIG10, TMEM25 and/or LSR Proteins on Cells Isolated from Draining Lymph Nodes and Spleens of Tumor Bearing Mice

(i) Expression validation of LY6G6F, VSIG10, TMEM25 and/or LSR proteins using specific antibodies directed against LY6G6F, VSIG10, TMEM25 and/or LSR proteins, respectively, is done on epithelial cancer cells as well as on immune cells from tumor draining lymph nodes vs. spleen of tumor bearing C57 mice, as described in Clinical Cancer Research 1996 Vol. 2, 811-820. Three different cancer types are being tested: B 16 (melanoma), ID8 (ovarian) and MC38 (colon)), to show expression of any of LY6G6F, VSIG10, TMEM25 and/or LSR in tumor cells and in immune cells in the tumor draining lymph node.

ii) Binding assay with mouse LY6G6F, VSIG10, TMEM25 and/or LSR ECD-FC proteins on cells isolated from epithelial cancer as well as on immune cells from tumor draining lymph nodes versus spleen of tumor bearing C57 mice, is carried out as described above, to show expression of the counter receptor for any of LY6G6F, VSIG10, TMEM25 and/or LSR in tumor cells and in immune cells in the tumor draining lymph node.

c) Expression of LY6G6F, VSIG10, TMEM25 and/or LSR Proteins on M2 Polarized Macrophages

(i) Expression validation of LY6G6F, VSIG10, TMEM25 and/or LSR proteins using specific antibodies directed against LY6G6F, VSIG10, TMEM25 and/or LSR proteins, respectively, is done on primary monocytes isolated from peripheral blood, differentiated into macrophages and exposed to "M2 driving stimuli" (e.g. IL4, IL10, Glucocorticoids, TGF beta), as described in Nat. Immunol. 2010; Vol. 11; p. 889-896, to show expression of any of LY6G6F, VSIG10, TMEM25 and/or LSR in M2 differentiated Macrophages.

ii) Binding assay with LY6G6F, VSIG10, TMEM25 and/or LSR human ECD-FC proteins on primary monocytes isolated from peripheral blood, differentiated into macrophages and exposed to "M2 driving stimuli" (e.g. IL4, IL10, Glucocorticoids, TGF beta) is carried out as described above, to show expression of the counter receptor for any of LY6G6F, VSIG10, TMEM25 and/or LSR in M2 differentiated Macrophages.

Example 50

Development Of Fully Human Anti-LY6G6f, Anti-VSIG10, Anti-TMEM25 and/or Anti-LSR Antibodies

Generation Of Human Monoclonal Antibodies Against LY6G6F, VSIG10, TMEM25 and/or LSR Antigen

Fusion proteins composed of the extracellular domain of the LY6G6F, VSIG10, TMEM25 and/or LSR linked to a mouse IgG2 Fc polypeptide are generated by standard recombinant methods and used as antigen for immunization.

Transgenic HuMab Mouse.

Fully human monoclonal antibodies to LY6G6F, VSIG10, TMEM25 and/or LSR are prepared using mice from the HCo7 strain of the transgenic HuMab Mouse®, which expresses human antibody genes. In this mouse strain, the endogenous mouse kappa light chain gene has been homozygously disrupted as described in Chen et al. (1993) EMBO J. 12:811-820 and the endogenous mouse heavy chain gene has been homozygously disrupted as described in Example 1 of PCT Publication WO 01/09187. Furthermore, this mouse strain carries a human kappa light chain transgene, KCo5, as described in Fishwild et al. (1996) Nature Biotechnology 14:845-851, and a human heavy chain transgene, HCo7, as described in U.S. Pat. Nos. 5,545,806; 5,625,825; and 5,545,807.

HuMab Immunizations:

To generate fully human monoclonal antibodies to LY6G6F, VSIG10, TMEM25 and/or LSR, mice of the HCo7 HuMab Mouse strain can be immunized with purified recombinant LY6G6F, VSIG10, TMEM25 and/or LSR fusion protein derived from mammalian cells that are transfected with an expression vector containing the gene encoding the fusion protein. General immunization schemes for the HuMab Mouse are described in Lonberg, N. et al (1994) Nature 368(6474): 856-859; Fishwild, D. et al. (1996) Nature Biotechnology 14: 845-851 and PCT Publication WO 98/24884. The mice are 6-16 weeks of age upon the first infusion of antigen. A purified recombinant LY6G6F, VSIG10, TMEM25 and/or LSR antigen preparation (5-50 .mu.g, purified from transfected mammalian cells expressing LY6G6F, VSIG10, TMEM25 and/or LSR fusion protein) is used to immunize the HuMab mice intraperitoneally.

Transgenic mice are immunized twice with antigen in complete Freund's adjuvant or Ribi adjuvant IP, followed by 3-21 days IP (up to a total of 11 immunizations) with the antigen in incomplete Freund's or Ribi adjuvant. The immune response is monitored by retroorbital bleeds. The plasma is screened by ELISA (as described below), and mice with sufficient titers of anti-LY6G6F, VSIG10, TMEM25 and/or LSR human immunoglobulin are used for fusions. Mice are boosted intravenously with antigen 3 days before sacrifice and removal of the spleen.

Selection of HuMab mice producing anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR antibodies:

To select HuMab mice producing antibodies that bind LY6G6F, VSIG10, TMEM25 and/or LSR sera from immunized mice is tested by a modified ELISA as originally described by Fishwild, D. et al. (1996). Briefly, microtiter plates are coated with purified recombinant LY6G6F, VSIG10, TMEM25 and/or LSR fusion protein at 1-2 .mu.g/ml in PBS, 50 .mu.l/wells incubated 4 degrees C. overnight then blocked with 200 .mu.l/well of 5% BSA in PBS. Dilutions of plasma from LY6G6F, VSIG10, TMEM25 and/or LSR-immunized mice are added to each well and incubated for 1-2 hours at ambient temperature. The plates are washed with PBS/Tween and then incubated with a goat-anti-human kappa light chain polyclonal antibody conjugated with alkaline phosphatase for 1 hour at room temperature. After washing, the plates are developed with pNPP substrate and analyzed by spectrophotometer at OD 415-650. Mice that developed the highest titers of anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR antibodies are used for fusions. Fusions are performed as described below and hybridoma supernatants are tested for anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR activity by ELISA.

Generation of Hybridomas Producing Human Monoclonal Antibodies to LY6G6F, VSIG10, TMEM25 and/or LSR.

The mouse splenocytes, isolated from the HuMab mice, are fused with PEG to a mouse myeloma cell line based upon standard protocols. The resulting hybridomas are then screened for the production of antigen-specific antibodies. Single cell suspensions of splenic lymphocytes from immunized mice are fused to one-fourth the number of P3X63 Ag8.6.53 (ATCC CRL 1580) nonsecreting mouse myeloma cells with 50% PEG (Sigma). Cells are plated at approximately 1x10⁵/well in flat bottom microtiter plate, followed by about two week incubation in selective medium containing 10% fetal calf serum, supplemented with origen (IGEN) in RPMI, L-glutamine, sodium pyruvate, HEPES, penicillin, streptomycin, gentamycin, 1xHAT, and beta-mercaptoethanol. After 1-2 weeks, cells are cultured in medium in which the HAT is replaced with HT. Individual wells are then screened by ELISA (described above) for human anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR monoclonal IgG antibodies. Once extensive hybridoma growth occurred, medium is monitored usually after 10-14 days. The antibody secreting hybridomas are replated, screened again and, if still positive for human IgG, anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR monoclonal antibodies are subcloned at least twice by limiting dilution. The stable subclones are then cultured in vitro to generate small amounts of antibody in tissue culture medium for further characterization.

Hybridoma clones are selected for further analysis.

Structural Characterization Of Desired Anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR Human Monoclonal Antibodies

The cDNA sequences encoding the heavy and light chain variable regions of the obtained anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR monoclonal antibodies are obtained from the resultant hybridomas, respectively, using standard PCR techniques and are sequenced using standard DNA sequencing techniques.

The nucleotide and amino acid sequences of the heavy chain variable region and of the light chain variable region are identified. These sequences may be compared to known human germline immunoglobulin light and heavy chain sequences and the CDRs of each heavy and light of the obtained anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR sequences identified.

Characterization Of Binding Specificity And Binding Kinetics Of Anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR Human Monoclonal Antibodies

The binding affinity, binding kinetics, binding specificity, and cross-competition of anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR antibodies are examined by Biacore analysis. Also, binding specificity is examined by flow cytometry.

Binding Affinity and Kinetics

Anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR antibodies produced according to the invention are characterized for affinities and binding kinetics by Biacore analysis (Biacore AB, Uppsala, Sweden). Purified recombinant human LY6G6F, VSIG10, TMEM25 and/or LSR fusion protein is covalently linked to a CM5 chip (carboxy methyl dextran coated chip) via primary amines, using standard amine coupling chemistry and kit provided by Biacore. Binding is measured by flowing the antibodies in HBS EP buffer (provided by BIACore AB) at a concentration of 267 nM at a flow rate of 50 .mu.l/min. The antigen-association antibodies association kinetics is followed for 3 minutes and the dissociation kinetics is followed for 7 minutes. The association and

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dissociation curves are fit to a 1:1 Langmuir binding model using BIAevaluation software (Biacore AB). To minimize the effects of avidity in the estimation of the binding constants, only the initial segment of data corresponding to association and dissociation phases are used for fitting.

Epitope Mapping of Obtained anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR Antibodies

Biacore is used to determine epitope grouping of anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR HuMAbs. Obtained anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR antibodies are used to map their epitopes on the LY6G6F, VSIG10, TMEM25 and/or LSR antigen, respectively. These different antibodies are coated on three different surfaces of the same chip to 8000 RUs each. Dilutions of each of the mAbs are made, starting at 10 $\mu\text{g}/\text{mL}$ and is incubated with Fc fused LY6G6F, VSIG10, TMEM25 and/or LSR (50 nM) for one hour. The incubated complex is injected over all the three surfaces (and a blank surface) at the same time for 1.5 minutes at a flow rate of 20 $\mu\text{L}/\text{min}$. Signal from each surface at end of 1.5 minutes, after subtraction of appropriate blanks, has been plotted against concentration of mAb in the complex. Upon analysis of the data, the anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR antibodies are categorized into different epitope groups depending on the epitope mapping results. The functional properties thereof are also compared.

Chinese hamster ovary (CHO) cell lines that express LY6G6F, VSIG10, TMEM25 and/or LSR protein at the cell surface are developed and used to determine the specificity of the LY6G6F, VSIG10, TMEM25 and/or LSR HuMAbs by flow cytometry. CHO cells are transfected with expression plasmids containing full length cDNA encoding a transmembrane forms of LY6G6F, VSIG10, TMEM25 and/or LSR antigen or a variant thereof. The transfected proteins con-

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tained an epitope tag at the N-terminus are used for detection by an antibody specific for the epitope. Binding of a anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR MAb is assessed by incubating the transfected cells with each of the LY6G6F, VSIG10, TMEM25 and/or LSR Abs at a concentration of 10 $\mu\text{g}/\text{mL}$. The cells are washed and binding is detected with a FITC-labeled anti-human IgG Ab. A murine anti-epitope tag Ab, followed by labeled anti-murine IgG, is used as the positive control. Non-specific human and murine Abs are used as negative controls. The obtained data is used to assess the specificity of the HuMAbs for the LY6G6F, VSIG10, TMEM25 and/or LSR antigen target.

These antibodies and other antibodies specific to LY6G6F, VSIG10, TMEM25 and/or LSR may be used in the afore-described anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR related therapies such as treatment of cancers wherein LY6G6F, VSIG10, TMEM25 and/or LSR antigen is differentially expressed and/or for modulating (enhancing or inhibiting) B7 immune co-stimulation involving the LY6G6F, VSIG10, TMEM25 and/or LSR antigen such as in the treatment of cancers and autoimmune diseases wherein such antibodies will e.g., prevent negative stimulation of T cell activity against desired target cancer cells or prevent the positive stimulation of T cell activity thereby eliciting a desired anti-autoimmune effect.

The invention has been described and various embodiments provided relating to manufacture and selection of desired anti-LY6G6F, anti-VSIG10, anti-TMEM25 and/or anti-LSR antibodies for use as therapeutics and diagnostic methods wherein the disease or condition is associated with LY6G6F, VSIG10, TMEM25 and/or LSR antigen. Different embodiments may optionally be combined herein in any suitable manner, beyond those explicit combinations and sub-combinations shown herein. The invention is now further described by the claims which follow.

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Arg Trp Asp Gly Gly Tyr Pro Asp Pro Asp Phe Leu Trp Ile Glu Glu
 145 150 155 160
 Pro Gly Gly Val Ile Val Gly Lys Ser Lys Leu Gly Val Glu Met Leu
 165 170 175
 Ser Glu Ser Gln Leu Ser Asp Gly Lys Lys Phe Lys Cys Val Thr Ser
 180 185 190
 His Ile Val Gly Pro Glu Ser Gly Ala Ser Cys Met Val Gln Ile Arg
 195 200 205
 Gly Pro Ser Leu Leu Ser Glu Pro Met Lys Thr Cys Phe Thr Gly Gly
 210 215 220
 Asn Val Thr Leu Thr Cys Gln Val Ser Gly Ala Tyr Pro Pro Ala Lys
 225 230 235 240
 Ile Leu Trp Leu Arg Asn Leu Thr Gln Pro Glu Val Ile Ile Gln Pro
 245 250 255
 Ser Ser Arg His Leu Ile Thr Gln Asp Gly Gln Asn Ser Thr Leu Thr
 260 265 270
 Ile His Asn Cys Ser Gln Asp Leu Asp Glu Gly Tyr Tyr Ile Cys Arg
 275 280 285
 Ala Asp Ser Pro Val Gly Val Arg Glu Met Glu Ile Trp Leu Ser Val
 290 295 300
 Lys Glu Pro Leu Asn Ile Gly Gly Ile Val Gly Thr Ile Val Ser Leu
 305 310 315 320
 Leu Leu Leu Gly Leu Ala Ile Ile Ser Gly Leu Leu Leu His Tyr Ser
 325 330 335
 Pro Val Phe Cys Trp Lys Val Gly Asn Thr Ser Arg Gly Gln Asn Met
 340 345 350
 Asp Asp Val Met Val Leu Val Asp Ser Glu Glu Glu Glu Glu Glu
 355 360 365
 Glu Glu Glu Glu Glu Asp Ala Ala Val Gly Glu Gln Glu Gly Ala Arg
 370 375 380
 Glu Arg Glu Glu Leu Pro Lys Glu Ile Pro Lys Gln Asp His Ile His
 385 390 395 400
 Arg Val Thr Ala Leu Val Asn Gly Asn Ile Glu Gln Met Gly Asn Gly
 405 410 415
 Phe Gln Asp Leu Gln Asp Asp Ser Ser Glu Glu Gln Ser Asp Ile Val
 420 425 430
 Gln Glu Glu Asp Arg Pro Val
 435

<210> SEQ ID NO 6
 <211> LENGTH: 282
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 6

Val Val Ile Gly Glu Val His Glu Asn Val Thr Leu His Cys Gly Asn
 1 5 10 15
 Ile Ser Gly Leu Arg Gly Gln Val Thr Trp Tyr Arg Asn Asn Ser Glu
 20 25 30
 Pro Val Phe Leu Leu Ser Ser Asn Ser Ser Leu Arg Pro Ala Glu Pro
 35 40 45
 Arg Phe Ser Leu Val Asp Ala Thr Ser Leu His Ile Glu Ser Leu Ser
 50 55 60

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Leu Gly Asp Glu Gly Ile Tyr Thr Cys Gln Glu Ile Leu Asn Val Thr
 65 70 75 80
 Gln Trp Phe Gln Val Trp Leu Gln Val Ala Asn Pro Pro Pro Ser Ala
 85 90 95
 Pro Gln Cys Trp Ala Gln Met Ala Ser Gly Ser Phe Met Leu Gln Leu
 100 105 110
 Thr Cys Arg Trp Asp Gly Gly Tyr Pro Asp Pro Asp Phe Leu Trp Ile
 115 120 125
 Glu Glu Pro Gly Gly Val Ile Val Gly Lys Ser Lys Leu Gly Val Glu
 130 135 140
 Met Leu Ser Glu Ser Gln Leu Ser Asp Gly Lys Lys Phe Lys Cys Val
 145 150 155 160
 Thr Ser His Ile Val Gly Pro Glu Ser Gly Ala Ser Cys Met Val Gln
 165 170 175
 Ile Arg Gly Pro Ser Leu Leu Ser Glu Pro Met Lys Thr Cys Phe Thr
 180 185 190
 Gly Gly Asn Val Thr Leu Thr Cys Gln Val Ser Gly Ala Tyr Pro Pro
 195 200 205
 Ala Lys Ile Leu Trp Leu Arg Asn Leu Thr Gln Pro Glu Val Ile Ile
 210 215 220
 Gln Pro Ser Ser Arg His Leu Ile Thr Gln Asp Gly Gln Asn Ser Thr
 225 230 235 240
 Leu Thr Ile His Asn Cys Ser Gln Asp Leu Asp Glu Gly Tyr Tyr Ile
 245 250 255
 Cys Arg Ala Asp Ser Pro Val Gly Val Arg Glu Met Glu Ile Trp Leu
 260 265 270
 Ser Val Lys Glu Pro Leu Asn Ile Gly Gly
 275 280

<210> SEQ ID NO 7
 <211> LENGTH: 366
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 7

Met Ala Leu Pro Pro Gly Pro Ala Ala Leu Arg His Thr Leu Leu Leu
 1 5 10 15
 Leu Pro Ala Leu Leu Ser Ser Gly Trp Gly Glu Leu Glu Pro Gln Ile
 20 25 30
 Asp Gly Gln Thr Trp Ala Glu Arg Ala Leu Arg Glu Asn Glu Arg His
 35 40 45
 Ala Phe Thr Cys Arg Val Ala Gly Gly Pro Gly Thr Pro Arg Leu Ala
 50 55 60
 Trp Tyr Leu Asp Gly Gln Leu Gln Glu Ala Ser Thr Ser Arg Leu Leu
 65 70 75 80
 Ser Val Gly Gly Glu Ala Phe Ser Gly Gly Thr Ser Thr Phe Thr Val
 85 90 95
 Thr Ala His Arg Ala Gln His Glu Leu Asn Cys Ser Leu Gln Asp Pro
 100 105 110
 Arg Ser Gly Arg Ser Ala Asn Ala Ser Val Ile Leu Asn Val Gln Phe
 115 120 125
 Lys Pro Glu Ile Ala Gln Val Gly Ala Lys Tyr Gln Glu Ala Gln Gly
 130 135 140

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Pro Gly Leu Leu Val Val Leu Phe Ala Leu Val Arg Ala Asn Pro Pro
 145 150 155 160
 Ala Asn Val Thr Trp Ile Asp Gln Asp Gly Pro Val Thr Val Asn Thr
 165 170 175
 Ser Asp Phe Leu Val Leu Asp Ala Gln Asn Tyr Pro Trp Leu Thr Asn
 180 185 190
 His Thr Val Gln Leu Gln Leu Arg Ser Leu Ala His Asn Leu Ser Val
 195 200 205
 Val Ala Thr Asn Asp Val Gly Val Thr Ser Ala Ser Leu Pro Ala Pro
 210 215 220
 Gly Leu Leu Ala Thr Arg Val Glu Val Pro Leu Leu Gly Ile Val Val
 225 230 235 240
 Ala Ala Gly Leu Ala Leu Gly Thr Leu Val Gly Phe Ser Thr Leu Val
 245 250 255
 Ala Cys Leu Val Cys Arg Lys Glu Lys Lys Thr Lys Gly Pro Ser Arg
 260 265 270
 His Pro Ser Leu Ile Ser Ser Asp Ser Asn Asn Leu Lys Leu Asn Asn
 275 280 285
 Val Arg Leu Pro Arg Glu Asn Met Ser Leu Pro Ser Asn Leu Gln Leu
 290 295 300
 Asn Asp Leu Thr Pro Asp Ser Arg Ala Val Lys Pro Ala Asp Arg Gln
 305 310 315 320
 Met Ala Gln Asn Asn Ser Arg Pro Glu Leu Leu Asp Pro Glu Pro Gly
 325 330 335
 Gly Leu Leu Thr Ser Gln Gly Phe Ile Arg Leu Pro Val Leu Gly Tyr
 340 345 350
 Ile Tyr Arg Val Ser Ser Val Ser Ser Asp Glu Ile Trp Leu
 355 360 365

<210> SEQ ID NO 8
 <211> LENGTH: 206
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 8

Glu Leu Glu Pro Gln Ile Asp Gly Gln Thr Trp Ala Glu Arg Ala Leu
 1 5 10 15
 Arg Glu Asn Glu Arg His Ala Phe Thr Cys Arg Val Ala Gly Gly Pro
 20 25 30
 Gly Thr Pro Arg Leu Ala Trp Tyr Leu Asp Gly Gln Leu Gln Glu Ala
 35 40 45
 Ser Thr Ser Arg Leu Leu Ser Val Gly Gly Glu Ala Phe Ser Gly Gly
 50 55 60
 Thr Ser Thr Phe Thr Val Thr Ala His Arg Ala Gln His Glu Leu Asn
 65 70 75 80
 Cys Ser Leu Gln Asp Pro Arg Ser Gly Arg Ser Ala Asn Ala Ser Val
 85 90 95
 Ile Leu Asn Val Gln Phe Lys Pro Glu Ile Ala Gln Val Gly Ala Lys
 100 105 110
 Tyr Gln Glu Ala Gln Gly Pro Gly Leu Leu Val Val Leu Phe Ala Leu
 115 120 125
 Val Arg Ala Asn Pro Pro Ala Asn Val Thr Trp Ile Asp Gln Asp Gly
 130 135 140

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Pro Val Thr Val Asn Thr Ser Asp Phe Leu Val Leu Asp Ala Gln Asn
 145 150 155 160
 Tyr Pro Trp Leu Thr Asn His Thr Val Gln Leu Gln Leu Arg Ser Leu
 165 170 175
 Ala His Asn Leu Ser Val Val Ala Thr Asn Asp Val Gly Val Thr Ser
 180 185 190
 Ala Ser Leu Pro Ala Pro Gly Leu Leu Ala Thr Arg Val Glu
 195 200 205

<210> SEQ ID NO 9
 <211> LENGTH: 232
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 9

Met Glu Leu Pro Leu Ser Gln Ala Thr Leu Arg His Thr Leu Leu Leu
 1 5 10 15
 Leu Pro Ala Leu Leu Ser Ser Gly Gln Gly Glu Leu Ala Pro Gln Ile
 20 25 30
 Asp Gly Gln Thr Trp Ala Glu Arg Ala Leu Arg Glu Asn Glu His His
 35 40 45
 Ala Phe Thr Cys Arg Val Ala Gly Gly Ser Ala Thr Pro Arg Leu Ala
 50 55 60
 Trp Tyr Leu Asp Gly Gln Leu Gln Glu Ala Thr Thr Ser Arg Leu Leu
 65 70 75 80
 Ser Val Gly Gly Asp Ala Phe Ser Gly Gly Thr Ser Thr Phe Thr Val
 85 90 95
 Thr Ala Gln Arg Ser Gln His Glu Leu Asn Cys Ser Leu Gln Asp Pro
 100 105 110
 Gly Ser Gly Arg Pro Ala Asn Ala Ser Val Ile Leu Asn Val Gln Phe
 115 120 125
 Lys Pro Glu Ile Ala Gln Val Gly Ala Lys Tyr Gln Glu Ala Gln Gly
 130 135 140
 Pro Gly Leu Leu Val Val Leu Phe Ala Leu Val Arg Ala Asn Pro Pro
 145 150 155 160
 Ala Asn Val Thr Trp Ile Asp Gln Asp Gly Pro Val Thr Val Asn Ala
 165 170 175
 Ser Asp Phe Leu Val Leu Asp Ala Gln Asn Tyr Pro Trp Leu Thr Asn
 180 185 190
 His Thr Val Gln Leu Gln Leu Arg Ser Leu Ala His Asn Leu Ser Val
 195 200 205
 Val Ala Thr Asn Asp Val Gly Val Thr Ser Ala Ser Leu Pro Ala Pro
 210 215 220
 Gly Leu Leu Ala Thr Arg Ile Glu
 225 230

<210> SEQ ID NO 10
 <211> LENGTH: 211
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 10

Met Ala Leu Leu Ala Gly Gly Leu Ser Arg Gly Leu Gly Ser His Pro

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1	5	10	15
Ala Ala Ala Gly Arg Asp Ala Val Val Phe Val Trp Leu Leu Leu Ser	20	25	30
Thr Trp Cys Thr Ala Pro Ala Arg Ala Ile Gln Val Thr Val Ser Asn	35	40	45
Pro Tyr His Val Val Ile Leu Phe Gln Pro Val Thr Leu Pro Cys Thr	50	55	60
Tyr Gln Met Thr Ser Thr Pro Thr Gln Pro Ile Val Ile Trp Lys Tyr	65	70	80
Lys Ser Phe Cys Arg Asp Arg Ile Ala Asp Ala Phe Ser Pro Ala Ser	85	90	95
Val Asp Asn Gln Leu Asn Ala Gln Leu Ala Ala Gly Asn Pro Gly Tyr	100	105	110
Asn Pro Tyr Val Glu Cys Gln Asp Ser Val Arg Thr Val Arg Val Val	115	120	125
Ala Thr Lys Gln Gly Asn Ala Val Thr Leu Gly Asp Tyr Tyr Gln Gly	130	135	140
Arg Arg Ile Thr Ile Thr Gly Asn Ala Asp Leu Thr Phe Asp Gln Thr	145	150	160
Ala Trp Gly Asp Ser Gly Val Tyr Tyr Cys Ser Val Val Ser Ala Gln	165	170	175
Asp Leu Gln Gly Asn Asn Glu Ala Tyr Ala Glu Leu Ile Val Leu Gly	180	185	190
Arg Thr Ser Gly Val Ala Glu Leu Leu Pro Gly Phe Gln Ala Gly Pro	195	200	205
Ile Glu Asp	210		

<210> SEQ ID NO 11

<211> LENGTH: 601

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 11

Met Ala Leu Leu Ala Gly Gly Leu Ser Arg Gly Leu Gly Ser His Pro	1	5	10	15
Ala Ala Ala Gly Arg Asp Ala Val Val Phe Val Trp Leu Leu Leu Ser	20	25	30	
Thr Trp Cys Thr Ala Pro Ala Arg Ala Ile Gln Val Thr Val Ser Asn	35	40	45	
Pro Tyr His Val Val Ile Leu Phe Gln Pro Val Thr Leu Pro Cys Thr	50	55	60	
Tyr Gln Met Thr Ser Thr Pro Thr Gln Pro Ile Val Ile Trp Lys Tyr	65	70	75	80
Lys Ser Phe Cys Arg Asp Arg Ile Ala Asp Ala Phe Ser Pro Ala Ser	85	90	95	
Val Asp Asn Gln Leu Asn Ala Gln Leu Ala Ala Gly Asn Pro Gly Tyr	100	105	110	
Asn Pro Tyr Val Glu Cys Gln Asp Ser Val Arg Thr Val Arg Val Val	115	120	125	
Ala Thr Lys Gln Gly Asn Ala Val Thr Leu Gly Asp Tyr Tyr Gln Gly	130	135	140	
Arg Arg Ile Thr Ile Thr Gly Asn Ala Asp Leu Thr Phe Asp Gln Thr				

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145					150					155					160
Ala	Trp	Gly	Asp	Ser	Gly	Val	Tyr	Tyr	Cys	Ser	Val	Val	Ser	Ala	Gln
				165					170					175	
Asp	Leu	Gln	Gly	Asn	Asn	Glu	Ala	Tyr	Ala	Glu	Leu	Ile	Val	Leu	Gly
			180					185					190		
Arg	Thr	Ser	Gly	Val	Ala	Glu	Leu	Leu	Pro	Gly	Phe	Gln	Ala	Gly	Pro
		195					200					205			
Ile	Glu	Asp	Trp	Leu	Phe	Val	Val	Val	Val	Cys	Leu	Ala	Ala	Phe	Leu
	210					215					220				
Ile	Phe	Leu	Leu	Leu	Gly	Ile	Cys	Trp	Cys	Gln	Cys	Cys	Pro	His	Thr
225					230					235					240
Cys	Cys	Cys	Tyr	Val	Arg	Cys	Pro	Cys	Cys	Pro	Asp	Lys	Cys	Cys	Cys
				245					250					255	
Pro	Glu	Ala	Leu	Tyr	Ala	Ala	Gly	Lys	Ala	Ala	Thr	Ser	Gly	Val	Pro
			260					265					270		
Ser	Ile	Tyr	Ala	Pro	Ser	Thr	Tyr	Ala	His	Leu	Ser	Pro	Ala	Lys	Thr
		275					280					285			
Pro	Pro	Pro	Pro	Ala	Met	Ile	Pro	Met	Gly	Pro	Ala	Tyr	Asn	Gly	Tyr
	290					295					300				
Pro	Gly	Gly	Tyr	Pro	Gly	Asp	Val	Asp	Arg	Ser	Ser	Ser	Ala	Gly	Gly
305					310					315					320
Gln	Gly	Ser	Tyr	Val	Pro	Leu	Leu	Arg	Asp	Thr	Asp	Ser	Ser	Val	Ala
				325					330					335	
Ser	Glu	Val	Arg	Ser	Gly	Tyr	Arg	Ile	Gln	Ala	Ser	Gln	Gln	Asp	Asp
		340						345					350		
Ser	Met	Arg	Val	Leu	Tyr	Tyr	Met	Glu	Lys	Glu	Leu	Ala	Asn	Phe	Asp
		355					360					365			
Pro	Ser	Arg	Pro	Gly	Pro	Pro	Ser	Gly	Arg	Val	Glu	Arg	Ala	Met	Ser
	370					375					380				
Glu	Val	Thr	Ser	Leu	His	Glu	Asp	Asp	Trp	Arg	Ser	Arg	Pro	Ser	Arg
385					390					395					400
Gly	Pro	Ala	Leu	Thr	Pro	Ile	Arg	Asp	Glu	Glu	Trp	Gly	Gly	His	Ser
				405					410					415	
Pro	Arg	Ser	Pro	Arg	Gly	Trp	Asp	Gln	Glu	Pro	Ala	Arg	Glu	Gln	Ala
			420					425					430		
Gly	Gly	Gly	Trp	Arg	Ala	Arg	Arg	Pro	Arg	Ala	Arg	Ser	Val	Asp	Ala
		435					440					445			
Leu	Asp	Asp	Leu	Thr	Pro	Pro	Ser	Thr	Ala	Glu	Ser	Gly	Ser	Arg	Ser
	450					455					460				
Pro	Thr	Ser	Asn	Gly	Gly	Arg	Ser	Arg	Ala	Tyr	Met	Pro	Pro	Arg	Ser
465					470					475					480
Arg	Ser	Arg	Asp	Asp	Leu	Tyr	Asp	Gln	Asp	Asp	Ser	Arg	Asp	Phe	Pro
				485					490					495	
Arg	Ser	Arg	Asp	Pro	His	Tyr	Asp	Asp	Phe	Arg	Ser	Arg	Glu	Arg	Pro
				500				505					510		
Pro	Ala	Asp	Pro	Arg	Ser	His	His	His	Arg	Thr	Arg	Asp	Pro	Arg	Asp
		515					520					525			
Asn	Gly	Ser	Arg	Ser	Gly	Asp	Leu	Pro	Tyr	Asp	Gly	Arg	Leu	Leu	Glu
	530					535					540				
Glu	Ala	Val	Arg	Lys	Lys	Gly	Ser	Glu	Glu	Arg	Arg	Arg	Pro	His	Lys
545					550					555					560
Glu	Glu	Glu	Glu	Glu	Ala	Tyr	Tyr	Pro	Pro	Ala	Pro	Pro	Pro	Tyr	Ser
				565					570					575	

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Glu Thr Asp Ser Gln Ala Ser Arg Glu Arg Arg Leu Lys Lys Asn Leu
 580 585 590

Ala Leu Ser Arg Glu Ser Leu Val Val
 595 600

<210> SEQ ID NO 12
 <211> LENGTH: 170
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 12

Ile Gln Val Thr Val Ser Asn Pro Tyr His Val Val Ile Leu Phe Gln
 1 5 10 15
 Pro Val Thr Leu Pro Cys Thr Tyr Gln Met Thr Ser Thr Pro Thr Gln
 20 25 30
 Pro Ile Val Ile Trp Lys Tyr Lys Ser Phe Cys Arg Asp Arg Ile Ala
 35 40 45
 Asp Ala Phe Ser Pro Ala Ser Val Asp Asn Gln Leu Asn Ala Gln Leu
 50 55 60
 Ala Ala Gly Asn Pro Gly Tyr Asn Pro Tyr Val Glu Cys Gln Asp Ser
 65 70 75 80
 Val Arg Thr Val Arg Val Val Ala Thr Lys Gln Gly Asn Ala Val Thr
 85 90 95
 Leu Gly Asp Tyr Tyr Gln Gly Arg Arg Ile Thr Ile Thr Gly Asn Ala
 100 105 110
 Asp Leu Thr Phe Asp Gln Thr Ala Trp Gly Asp Ser Gly Val Tyr Tyr
 115 120 125
 Cys Ser Val Val Ser Ala Gln Asp Leu Gln Gly Asn Asn Glu Ala Tyr
 130 135 140
 Ala Glu Leu Ile Val Leu Gly Arg Thr Ser Gly Val Ala Glu Leu Leu
 145 150 155 160
 Pro Gly Phe Gln Ala Gly Pro Ile Glu Asp
 165 170

<210> SEQ ID NO 13
 <211> LENGTH: 582
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 13

Met Ala Leu Leu Ala Gly Gly Leu Ser Arg Gly Leu Gly Ser His Pro
 1 5 10 15
 Ala Ala Ala Gly Arg Asp Ala Val Val Phe Val Trp Leu Leu Leu Ser
 20 25 30
 Thr Trp Cys Thr Ala Pro Ala Arg Ala Ile Gln Val Thr Val Ser Asn
 35 40 45
 Pro Tyr His Val Val Ile Leu Phe Gln Pro Val Thr Leu Pro Cys Thr
 50 55 60
 Tyr Gln Met Thr Ser Thr Pro Thr Gln Pro Ile Val Ile Trp Lys Tyr
 65 70 75 80
 Lys Ser Phe Cys Arg Asp Arg Ile Ala Asp Ala Phe Ser Pro Ala Ser
 85 90 95
 Val Asp Asn Gln Leu Asn Ala Gln Leu Ala Ala Gly Asn Pro Gly Tyr

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100					105					110				
Asn	Pro	Tyr	Val	Glu	Cys	Gln	Asp	Ser	Val	Arg	Thr	Val	Arg	Val
	115						120					125		
Ala	Thr	Lys	Gln	Gly	Asn	Ala	Val	Thr	Leu	Gly	Asp	Tyr	Tyr	Gln
	130					135					140			Gly
Arg	Arg	Ile	Thr	Ile	Thr	Gly	Asn	Ala	Asp	Leu	Thr	Phe	Asp	Gln
	145					150					155			160
Ala	Trp	Gly	Asp	Ser	Gly	Val	Tyr	Tyr	Cys	Ser	Val	Val	Ser	Ala
			165						170					175
Asp	Leu	Gln	Gly	Asn	Asn	Glu	Ala	Tyr	Ala	Glu	Leu	Ile	Val	Leu
		180						185					190	Asp
Trp	Leu	Phe	Val	Val	Val	Val	Cys	Leu	Ala	Ala	Phe	Leu	Ile	Phe
	195						200					205		Leu
Leu	Leu	Gly	Ile	Cys	Trp	Cys	Gln	Cys	Cys	Pro	His	Thr	Cys	Cys
	210					215					220			Cys
Tyr	Val	Arg	Cys	Pro	Cys	Cys	Pro	Asp	Lys	Cys	Cys	Cys	Pro	Glu
	225				230					235				240
Leu	Tyr	Ala	Ala	Gly	Lys	Ala	Ala	Thr	Ser	Gly	Val	Pro	Ser	Ile
			245						250					255
Ala	Pro	Ser	Thr	Tyr	Ala	His	Leu	Ser	Pro	Ala	Lys	Thr	Pro	Pro
		260						265					270	
Pro	Ala	Met	Ile	Pro	Met	Gly	Pro	Ala	Tyr	Asn	Gly	Tyr	Pro	Gly
	275					280						285		Gly
Tyr	Pro	Gly	Asp	Val	Asp	Arg	Ser	Ser	Ser	Ala	Gly	Gly	Gln	Gly
	290					295					300			Ser
Tyr	Val	Pro	Leu	Leu	Arg	Asp	Thr	Asp	Ser	Ser	Val	Ala	Ser	Glu
	305				310					315				320
Arg	Ser	Gly	Tyr	Arg	Ile	Gln	Ala	Ser	Gln	Gln	Asp	Asp	Ser	Met
			325						330					335
Val	Leu	Tyr	Tyr	Met	Glu	Lys	Glu	Leu	Ala	Asn	Phe	Asp	Pro	Ser
		340						345					350	Arg
Pro	Gly	Pro	Pro	Ser	Gly	Arg	Val	Glu	Arg	Ala	Met	Ser	Glu	Val
	355					360						365		Thr
Ser	Leu	His	Glu	Asp	Asp	Trp	Arg	Ser	Arg	Pro	Ser	Arg	Gly	Pro
	370					375					380			Ala
Leu	Thr	Pro	Ile	Arg	Asp	Glu	Glu	Trp	Gly	Gly	His	Ser	Pro	Arg
	385				390					395				400
Pro	Arg	Gly	Trp	Asp	Gln	Glu	Pro	Ala	Arg	Glu	Gln	Ala	Gly	Gly
			405						410					415
Trp	Arg	Ala	Arg	Arg	Pro	Arg	Ala	Arg	Ser	Val	Asp	Ala	Leu	Asp
		420						425					430	Asp
Leu	Thr	Pro	Pro	Ser	Thr	Ala	Glu	Ser	Gly	Ser	Arg	Ser	Pro	Thr
	435					440						445		Ser
Asn	Gly	Gly	Arg	Ser	Arg	Ala	Tyr	Met	Pro	Pro	Arg	Ser	Arg	Ser
	450					455					460			
Asp	Asp	Leu	Tyr	Asp	Gln	Asp	Asp	Ser	Arg	Asp	Phe	Pro	Arg	Ser
	465				470					475				480
Asp	Pro	His	Tyr	Asp	Asp	Phe	Arg	Ser	Arg	Glu	Arg	Pro	Pro	Ala
			485						490					495
Pro	Arg	Ser	His	His	His	Arg	Thr	Arg	Asp	Pro	Arg	Asp	Asn	Gly
			500					505					510	Ser
Arg	Ser	Gly	Asp	Leu	Pro	Tyr	Asp	Gly	Arg	Leu	Leu	Glu	Glu	Ala
		515					520					525		Val

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Arg Lys Lys Gly Ser Glu Glu Arg Arg Arg Pro His Lys Glu Glu Glu
530 535 540

Glu Glu Ala Tyr Tyr Pro Pro Ala Pro Pro Pro Tyr Ser Glu Thr Asp
545 550 555 560

Ser Gln Ala Ser Arg Glu Arg Arg Leu Lys Lys Asn Leu Ala Leu Ser
565 570 575

Arg Glu Ser Leu Val Val
580

<210> SEQ ID NO 14
 <211> LENGTH: 151
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 14

Ile Gln Val Thr Val Ser Asn Pro Tyr His Val Val Ile Leu Phe Gln
1 5 10 15

Pro Val Thr Leu Pro Cys Thr Tyr Gln Met Thr Ser Thr Pro Thr Gln
20 25 30

Pro Ile Val Ile Trp Lys Tyr Lys Ser Phe Cys Arg Asp Arg Ile Ala
35 40 45

Asp Ala Phe Ser Pro Ala Ser Val Asp Asn Gln Leu Asn Ala Gln Leu
50 55 60

Ala Ala Gly Asn Pro Gly Tyr Asn Pro Tyr Val Glu Cys Gln Asp Ser
65 70 75 80

Val Arg Thr Val Arg Val Val Ala Thr Lys Gln Gly Asn Ala Val Thr
85 90 95

Leu Gly Asp Tyr Tyr Gln Gly Arg Arg Ile Thr Ile Thr Gly Asn Ala
100 105 110

Asp Leu Thr Phe Asp Gln Thr Ala Trp Gly Asp Ser Gly Val Tyr Tyr
115 120 125

Cys Ser Val Val Ser Ala Gln Asp Leu Gln Gly Asn Asn Glu Ala Tyr
130 135 140

Ala Glu Leu Ile Val Leu Asp
145 150

<210> SEQ ID NO 15
 <211> LENGTH: 533
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 15

Met Ala Leu Leu Ala Gly Gly Leu Ser Arg Gly Leu Gly Ser His Pro
1 5 10 15

Ala Ala Ala Gly Arg Asp Ala Val Val Phe Val Trp Leu Leu Leu Ser
20 25 30

Thr Trp Cys Thr Ala Pro Ala Arg Ala Ile Gln Val Thr Val Ser Asn
35 40 45

Pro Tyr His Val Val Ile Leu Phe Gln Pro Val Thr Leu Pro Cys Thr
50 55 60

Tyr Gln Met Thr Ser Thr Pro Thr Gln Pro Ile Val Ile Trp Lys Tyr
65 70 75 80

Lys Ser Phe Cys Arg Asp Arg Ile Ala Asp Ala Phe Ser Pro Ala Ser

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85							90							95						
Val	Asp	Asn	Gln		Leu	Asn	Ala	Gln	Leu	Ala	Ala	Gly	Asn	Pro	Gly	Tyr				
			100																	
Asn	Pro	Tyr	Val	Glu	Cys	Gln		Asp	Ser	Val	Arg	Thr	Val	Arg	Val	Val				
			115																	
Ala	Thr	Lys	Gln	Gly	Asn	Ala	Val	Thr	Leu	Gly	Asp	Tyr	Tyr	Gln	Gly					
			130																	
Arg	Arg	Ile	Thr	Ile	Thr	Gly	Asn	Ala	Asp	Leu	Thr	Phe	Asp	Gln	Thr					
			145																	
Ala	Trp	Gly	Asp	Ser	Gly	Val	Tyr	Tyr	Cys	Ser	Val	Val	Ser	Ala	Gln					
			165																	
Asp	Leu	Gln	Gly	Asn	Asn	Glu	Ala	Tyr	Ala	Glu	Leu	Ile	Val	Leu	Val					
			180																	
Tyr	Ala	Ala	Gly	Lys	Ala	Ala	Thr	Ser	Gly	Val	Pro	Ser	Ile	Tyr	Ala					
			195																	
Pro	Ser	Thr	Tyr	Ala	His	Leu	Ser	Pro	Ala	Lys	Thr	Pro	Pro	Pro	Pro					
			210																	
Ala	Met	Ile	Pro	Met	Gly	Pro	Ala	Tyr	Asn	Gly	Tyr	Pro	Gly	Gly	Tyr					
			225																	
Pro	Gly	Asp	Val	Asp	Arg	Ser	Ser	Ser	Ala	Gly	Gly	Gln	Gly	Ser	Tyr					
			245																	
Val	Pro	Leu	Leu	Arg	Asp	Thr	Asp	Ser	Ser	Val	Ala	Ser	Glu	Val	Arg					
			260																	
Ser	Gly	Tyr	Arg	Ile	Gln	Ala	Ser	Gln	Gln	Asp	Asp	Ser	Met	Arg	Val					
			275																	
Leu	Tyr	Tyr	Met	Glu	Lys	Glu	Leu	Ala	Asn	Phe	Asp	Pro	Ser	Arg	Pro					
			290																	
Gly	Pro	Pro	Ser	Gly	Arg	Val	Glu	Arg	Ala	Met	Ser	Glu	Val	Thr	Ser					
			305																	
Leu	His	Glu	Asp	Asp	Trp	Arg	Ser	Arg	Pro	Ser	Arg	Gly	Pro	Ala	Leu					
			325																	
Thr	Pro	Ile	Arg	Asp	Glu	Glu	Trp	Gly	Gly	His	Ser	Pro	Arg	Ser	Pro					
			340																	
Arg	Gly	Trp	Asp	Gln	Glu	Pro	Ala	Arg	Glu	Gln	Ala	Gly	Gly	Gly	Trp					
			355																	
Arg	Ala	Arg	Arg	Pro	Arg	Ala	Arg	Ser	Val	Asp	Ala	Leu	Asp	Asp	Leu					
			370																	
Thr	Pro	Pro	Ser	Thr	Ala	Glu	Ser	Gly	Ser	Arg	Ser	Pro	Thr	Ser	Asn					
			385																	
Gly	Gly	Arg	Ser	Arg	Ala	Tyr	Met	Pro	Pro	Arg	Ser	Arg	Ser	Arg	Asp					
			405																	
Asp	Leu	Tyr	Asp	Gln	Asp	Asp	Ser	Arg	Asp	Phe	Pro	Arg	Ser	Arg	Asp					
			420																	
Pro	His	Tyr	Asp	Asp	Phe	Arg	Ser	Arg	Glu	Arg	Pro	Pro	Ala	Asp	Pro					
			435																	
Arg	Ser	His	His	His	Arg	Thr	Arg	Asp	Pro	Arg	Asp	Asn	Gly	Ser	Arg					
			450																	
Ser	Gly	Asp	Leu	Pro	Tyr	Asp	Gly	Arg	Leu	Leu	Glu	Glu	Ala	Val	Arg					
			465																	
Lys	Lys	Gly	Ser	Glu	Glu	Arg	Arg	Arg	Pro	His	Lys	Glu	Glu	Glu	Glu					
			485																	
Glu	Ala	Tyr	Tyr	Pro	Pro	Ala	Pro	Pro	Pro	Tyr	Ser	Glu	Thr	Asp	Ser					
			500																	

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Gln Ala Ser Arg Glu Arg Arg Leu Lys Lys Asn Leu Ala Leu Ser Arg
515 520 525

Glu Ser Leu Val Val
530

<210> SEQ ID NO 16
<211> LENGTH: 532
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 16

Met Ala Leu Leu Ala Gly Gly Leu Ser Arg Gly Leu Gly Ser His Pro
1 5 10 15

Ala Ala Ala Gly Arg Asp Ala Val Val Phe Val Trp Leu Leu Ser
20 25 30

Thr Trp Cys Thr Ala Pro Ala Arg Ala Ile Gln Val Thr Val Ser Asn
35 40 45

Pro Tyr His Val Val Ile Leu Phe Gln Pro Val Thr Leu Pro Cys Thr
50 55 60

Tyr Gln Met Thr Ser Thr Pro Thr Gln Pro Ile Val Ile Trp Lys Tyr
65 70 75 80

Lys Ser Phe Cys Arg Asp Arg Ile Ala Asp Ala Phe Ser Pro Ala Ser
85 90 95

Val Asp Asn Gln Leu Asn Ala Gln Leu Ala Ala Gly Asn Pro Gly Tyr
100 105 110

Asn Pro Tyr Val Glu Cys Gln Asp Ser Val Arg Thr Val Arg Val Val
115 120 125

Ala Thr Lys Gln Gly Asn Ala Val Thr Leu Gly Asp Tyr Tyr Gln Gly
130 135 140

Arg Arg Ile Thr Ile Thr Gly Asn Ala Asp Leu Thr Phe Asp Gln Thr
145 150 155 160

Ala Trp Gly Asp Ser Gly Val Tyr Tyr Cys Ser Val Val Ser Ala Gln
165 170 175

Asp Leu Gln Gly Asn Asn Glu Ala Tyr Ala Glu Leu Ile Val Leu Val
180 185 190

Tyr Ala Ala Gly Lys Ala Ala Thr Ser Gly Val Pro Ser Ile Tyr Ala
195 200 205

Pro Ser Thr Tyr Ala His Leu Ser Pro Ala Lys Thr Pro Pro Pro Pro
210 215 220

Ala Met Ile Pro Met Gly Pro Ala Tyr Asn Gly Tyr Pro Gly Gly Tyr
225 230 235 240

Pro Gly Asp Val Asp Arg Ser Ser Ser Ala Gly Gly Gln Gly Ser Tyr
245 250 255

Val Pro Leu Leu Arg Asp Thr Asp Ser Ser Val Ala Ser Val Arg Ser
260 265 270

Gly Tyr Arg Ile Gln Ala Ser Gln Gln Asp Asp Ser Met Arg Val Leu
275 280 285

Tyr Tyr Met Glu Lys Glu Leu Ala Asn Phe Asp Pro Ser Arg Pro Gly
290 295 300

Pro Pro Ser Gly Arg Val Glu Arg Ala Met Ser Glu Val Thr Ser Leu
305 310 315 320

His Glu Asp Asp Trp Arg Ser Arg Pro Ser Arg Gly Pro Ala Leu Thr
325 330 335

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Pro Ile Arg Asp Glu Glu Trp Gly Gly His Ser Pro Arg Ser Pro Arg
 340 345 350

Gly Trp Asp Gln Glu Pro Ala Arg Glu Gln Ala Gly Gly Gly Trp Arg
 355 360 365

Ala Arg Arg Pro Arg Ala Arg Ser Val Asp Ala Leu Asp Asp Leu Thr
 370 375 380

Pro Pro Ser Thr Ala Glu Ser Gly Ser Arg Ser Pro Thr Ser Asn Gly
 385 390 395 400

Gly Arg Ser Arg Ala Tyr Met Pro Pro Arg Ser Arg Ser Arg Asp Asp
 405 410 415

Leu Tyr Asp Gln Asp Asp Ser Arg Asp Phe Pro Arg Ser Arg Asp Pro
 420 425 430

His Tyr Asp Asp Phe Arg Ser Arg Glu Arg Pro Pro Ala Asp Pro Arg
 435 440 445

Ser His His His Arg Thr Arg Asp Pro Arg Asp Asn Gly Ser Arg Ser
 450 455 460

Gly Asp Leu Pro Tyr Asp Gly Arg Leu Leu Glu Glu Ala Val Arg Lys
 465 470 475 480

Lys Gly Ser Glu Glu Arg Arg Arg Pro His Lys Glu Glu Glu Glu Glu
 485 490 495

Ala Tyr Tyr Pro Pro Ala Pro Pro Pro Tyr Ser Glu Thr Asp Ser Gln
 500 505 510

Ala Ser Arg Glu Arg Arg Leu Lys Lys Asn Leu Ala Leu Ser Arg Glu
 515 520 525

Ser Leu Val Val
 530

<210> SEQ ID NO 17
 <211> LENGTH: 493
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 17

Met Ala Leu Leu Ala Gly Gly Leu Ser Arg Gly Leu Gly Ser His Pro
 1 5 10 15

Ala Ala Ala Gly Arg Asp Ala Val Val Phe Val Trp Leu Leu Leu Ser
 20 25 30

Thr Trp Cys Thr Ala Pro Ala Arg Ala Ile Gln Val Thr Val Ser Asn
 35 40 45

Pro Tyr His Val Val Ile Leu Phe Gln Pro Val Thr Leu Pro Cys Thr
 50 55 60

Tyr Gln Met Thr Ser Thr Pro Thr Gln Pro Ile Val Ile Trp Lys Tyr
 65 70 75 80

Lys Ser Phe Cys Arg Asp Arg Ile Ala Asp Ala Phe Ser Pro Ala Ser
 85 90 95

Val Asp Asn Gln Leu Asn Ala Gln Leu Ala Ala Gly Asn Pro Gly Tyr
 100 105 110

Asn Pro Tyr Val Glu Cys Gln Asp Ser Val Arg Thr Val Arg Val Val
 115 120 125

Ala Thr Lys Gln Gly Asn Ala Val Thr Leu Gly Asp Tyr Tyr Gln Gly
 130 135 140

Arg Arg Ile Thr Ile Thr Gly Met Tyr Ala Ala Gly Lys Ala Ala Thr
 145 150 155 160

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Ser Gly Val Pro Ser Ile Tyr Ala Pro Ser Thr Tyr Ala His Leu Ser
      165                      170                      175

Pro Ala Lys Thr Pro Pro Pro Pro Ala Met Ile Pro Met Gly Pro Ala
      180                      185                      190

Tyr Asn Gly Tyr Pro Gly Gly Tyr Pro Gly Asp Val Asp Arg Ser Ser
      195                      200                      205

Ser Ala Gly Gly Gln Gly Ser Tyr Val Pro Leu Leu Arg Asp Thr Asp
      210                      215                      220

Ser Ser Val Ala Ser Glu Val Arg Ser Gly Tyr Arg Ile Gln Ala Ser
      225                      230                      235                      240

Gln Gln Asp Asp Ser Met Arg Val Leu Tyr Tyr Met Glu Lys Glu Leu
      245                      250                      255

Ala Asn Phe Asp Pro Ser Arg Pro Gly Pro Pro Ser Gly Arg Val Glu
      260                      265                      270

Arg Ala Met Ser Glu Val Thr Ser Leu His Glu Asp Asp Trp Arg Ser
      275                      280                      285

Arg Pro Ser Arg Gly Pro Ala Leu Thr Pro Ile Arg Asp Glu Glu Trp
      290                      295                      300

Gly Gly His Ser Pro Arg Ser Pro Arg Gly Trp Asp Gln Glu Pro Ala
      305                      310                      315                      320

Arg Glu Gln Ala Gly Gly Gly Trp Arg Ala Arg Arg Pro Arg Ala Arg
      325                      330                      335

Ser Val Asp Ala Leu Asp Asp Leu Thr Pro Pro Ser Thr Ala Glu Ser
      340                      345                      350

Gly Ser Arg Ser Pro Thr Ser Asn Gly Gly Arg Ser Arg Ala Tyr Met
      355                      360                      365

Pro Pro Arg Ser Arg Ser Arg Asp Asp Leu Tyr Asp Gln Asp Asp Ser
      370                      375                      380

Arg Asp Phe Pro Arg Ser Arg Asp Pro His Tyr Asp Asp Phe Arg Ser
      385                      390                      395                      400

Arg Glu Arg Pro Pro Ala Asp Pro Arg Ser His His His Arg Thr Arg
      405                      410                      415

Asp Pro Arg Asp Asn Gly Ser Arg Ser Gly Asp Leu Pro Tyr Asp Gly
      420                      425                      430

Arg Leu Leu Glu Glu Ala Val Arg Lys Lys Gly Ser Glu Glu Arg Arg
      435                      440                      445

Arg Pro His Lys Glu Glu Glu Glu Glu Ala Tyr Tyr Pro Pro Ala Pro
      450                      455                      460

Pro Pro Tyr Ser Glu Thr Asp Ser Gln Ala Ser Arg Glu Arg Arg Leu
      465                      470                      475                      480

Lys Lys Asn Leu Ala Leu Ser Arg Glu Ser Leu Val Val
      485                      490

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<210> SEQ ID NO 18

<211> LENGTH: 552

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 18

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Met Ala Leu Leu Ala Gly Gly Leu Ser Arg Gly Leu Gly Ser His Pro
1          5          10          15

Ala Ala Ala Gly Arg Asp Ala Val Val Phe Val Trp Leu Leu Leu Ser
20          25          30

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Thr	Trp	Cys	Thr	Ala	Pro	Ala	Arg	Ala	Ile	Gln	Val	Thr	Val	Ser	Asn
		35					40					45			
Pro	Tyr	His	Val	Val	Ile	Leu	Phe	Gln	Pro	Val	Thr	Leu	Pro	Cys	Thr
	50					55					60				
Tyr	Gln	Met	Thr	Ser	Thr	Pro	Thr	Gln	Pro	Ile	Val	Ile	Trp	Lys	Tyr
65					70					75				80	
Lys	Ser	Phe	Cys	Arg	Asp	Arg	Ile	Ala	Asp	Ala	Phe	Ser	Pro	Ala	Ser
				85					90					95	
Val	Asp	Asn	Gln	Leu	Asn	Ala	Gln	Leu	Ala	Ala	Gly	Asn	Pro	Gly	Tyr
			100					105					110		
Asn	Pro	Tyr	Val	Glu	Cys	Gln	Asp	Ser	Val	Arg	Thr	Val	Arg	Val	Val
		115					120					125			
Ala	Thr	Lys	Gln	Gly	Asn	Ala	Val	Thr	Leu	Gly	Asp	Tyr	Tyr	Gln	Gly
	130					135					140				
Arg	Arg	Ile	Thr	Ile	Thr	Gly	Asn	Ala	Asp	Leu	Thr	Phe	Asp	Gln	Thr
145					150					155				160	
Ala	Trp	Gly	Asp	Ser	Gly	Val	Tyr	Tyr	Cys	Ser	Val	Val	Ser	Ala	Gln
				165					170					175	
Asp	Leu	Gln	Gly	Asn	Asn	Glu	Ala	Tyr	Ala	Glu	Leu	Ile	Val	Leu	Gly
		180						185					190		
Arg	Thr	Ser	Gly	Val	Ala	Glu	Leu	Leu	Pro	Gly	Phe	Gln	Ala	Gly	Pro
		195					200					205			
Ile	Glu	Val	Tyr	Ala	Ala	Gly	Lys	Ala	Ala	Thr	Ser	Gly	Val	Pro	Ser
	210					215					220				
Ile	Tyr	Ala	Pro	Ser	Thr	Tyr	Ala	His	Leu	Ser	Pro	Ala	Lys	Thr	Pro
225					230					235				240	
Pro	Pro	Pro	Ala	Met	Ile	Pro	Met	Gly	Pro	Ala	Tyr	Asn	Gly	Tyr	Pro
			245						250					255	
Gly	Gly	Tyr	Pro	Gly	Asp	Val	Asp	Arg	Ser	Ser	Ser	Ala	Gly	Gly	Gln
		260						265					270		
Gly	Ser	Tyr	Val	Pro	Leu	Leu	Arg	Asp	Thr	Asp	Ser	Ser	Val	Ala	Ser
		275					280					285			
Glu	Val	Arg	Ser	Gly	Tyr	Arg	Ile	Gln	Ala	Ser	Gln	Gln	Asp	Asp	Ser
		290				295					300				
Met	Arg	Val	Leu	Tyr	Tyr	Met	Glu	Lys	Glu	Leu	Ala	Asn	Phe	Asp	Pro
305					310					315				320	
Ser	Arg	Pro	Gly	Pro	Pro	Ser	Gly	Arg	Val	Glu	Arg	Ala	Met	Ser	Glu
			325						330					335	
Val	Thr	Ser	Leu	His	Glu	Asp	Asp	Trp	Arg	Ser	Arg	Pro	Ser	Arg	Gly
			340					345					350		
Pro	Ala	Leu	Thr	Pro	Ile	Arg	Asp	Glu	Glu	Trp	Gly	Gly	His	Ser	Pro
		355					360					365			
Arg	Ser	Pro	Arg	Gly	Trp	Asp	Gln	Glu	Pro	Ala	Arg	Glu	Gln	Ala	Gly
		370				375					380				
Gly	Gly	Trp	Arg	Ala	Arg										

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Ser Arg Asp Pro His Tyr Asp Asp Phe Arg Ser Arg Glu Arg Pro Pro
 450 455 460

Ala Asp Pro Arg Ser His His His Arg Thr Arg Asp Pro Arg Asp Asn
 465 470 475 480

Gly Ser Arg Ser Gly Asp Leu Pro Tyr Asp Gly Arg Leu Leu Glu Glu
 485 490 495

Ala Val Arg Lys Lys Gly Ser Glu Glu Arg Arg Arg Pro His Lys Glu
 500 505 510

Glu Glu Glu Glu Ala Tyr Tyr Pro Pro Ala Pro Pro Pro Tyr Ser Glu
 515 520 525

Thr Asp Ser Gln Ala Ser Arg Glu Arg Arg Leu Lys Lys Asn Leu Ala
 530 535 540

Leu Ser Arg Glu Ser Leu Val Val
 545 550

<210> SEQ ID NO 19
 <211> LENGTH: 429
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 19

Met Ala Gly Leu Arg Val Leu Leu Cys Leu Gly Ala Leu Leu Ala Arg
 1 5 10 15

Gln Gly Ser Ala Gly Leu Gln Leu Leu Leu Asn Pro Ser Arg Ala Asn
 20 25 30

Leu Ser Val Arg Pro Asn Ser Glu Val Leu Pro Gly Ile His Pro Asp
 35 40 45

Leu Glu Ala Val Ala Ile Gly Glu Val His Asp Asn Val Thr Leu Arg
 50 55 60

Cys Gly Ser Ala Ser Gly Ser Arg Gly Leu Val Thr Trp Tyr Arg Asn
 65 70 75 80

Asp Ser Glu Pro Ala Phe Leu Val Ser Phe Asn Ser Ser Leu Pro Pro
 85 90 95

Ala Ala Pro Arg Phe Ser Leu Glu Asp Ala Gly Ala Leu Arg Ile Glu
 100 105 110

Ala Leu Arg Leu Glu Asp Asp Gly Asn Tyr Thr Cys Gln Glu Val Leu
 115 120 125

Asn Glu Thr His Trp Phe Pro Val Arg Leu Arg Val Ala Ser Gly Pro
 130 135 140

Ala Tyr Val Glu Val Asn Ile Ser Ala Thr Gly Thr Leu Pro Asn Gly
 145 150 155 160

Thr Leu Tyr Ala Ala Arg Gly Ser Gln Val Asp Phe Asn Cys Cys Ser
 165 170 175

Ala Ala Gln Pro Pro Pro Glu Val Glu Trp Trp Ile Gln Thr His Ser
 180 185 190

Ile Pro Glu Phe Leu Gly Lys Asn Leu Ser Ala Asn Ser Phe Thr Leu
 195 200 205

Met Leu Met Ser Gln Asn Leu Gln Gly Asn Tyr Thr Cys Ser Ala Thr
 210 215 220

Asn Val Leu Ser Gly Arg Gln Arg Lys Val Thr Thr Glu Leu Leu Val
 225 230 235 240

Tyr Trp Pro Pro Pro Ser Ala Pro Gln Cys Ser Val Glu Val Ser Ser
 245 250 255

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Glu Ser Thr Thr Leu Glu Leu Ala Cys Asn Trp Asp Gly Gly Tyr Pro
 260 265 270
 Asp Pro Thr Phe Leu Trp Thr Glu Glu Pro Gly Gly Thr Ile Met Gly
 275 280 285
 Asn Ser Lys Leu Gln Thr Leu Ser Pro Ala Gln Leu Leu Glu Gly Lys
 290 295 300
 Lys Phe Lys Cys Val Gly Asn His Ile Leu Gly Pro Glu Ser Gly Ala
 305 310 315 320
 Ser Cys Val Val Lys Leu Ser Ser Pro Leu Leu Pro Ser Gln Pro Met
 325 330 335
 Arg Thr Cys Phe Val Gly Gly Asn Val Thr Leu Thr Cys Glu Val Ser
 340 345 350
 Gly Ala Asn Pro Pro Ala Arg Ile Gln Trp Leu Arg Asn Leu Thr Gln
 355 360 365
 Pro Ala Ile Gln Pro Ser Ser His Tyr Ile Ile Thr Gln Gln Gly Gln
 370 375 380
 Ser Ser Ser Leu Thr Ile His Asn Cys Ser Gln Asp Leu Asp Glu Gly
 385 390 395 400
 Phe Tyr Tyr Cys Gln Ala Glu Asn Leu Val Gly Val Arg Ala Thr Asn
 405 410 415
 Ile Trp Leu Ser Val Lys Glu Pro Leu Asn Ile Gly Gly
 420 425

<210> SEQ ID NO 20
 <211> LENGTH: 236
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 20

Met Ala Val Val Val Phe Leu Leu Phe Leu Cys Gly His Ser Gln Ala
 1 5 10 15
 Val Ala Asp Ser Ile Gln Thr Ile Tyr Val Ala Ser Gly Glu Ser Val
 20 25 30
 Glu Met Pro Cys Pro Ser Pro Pro Ser Leu Leu Gly Gly Gln Leu Leu
 35 40 45
 Thr Trp Phe Arg Ser Pro Val Ala Gly Ser Ser Thr Ile Leu Val Ala
 50 55 60
 Gln Val Gln Val Asp Lys Pro Val Ser Asp Leu Arg Lys Pro Glu Pro
 65 70 75 80
 Asp Ser Arg Tyr Lys Leu Phe Gly Asn Tyr Ser Leu Trp Leu Glu Gly
 85 90 95
 Ser Arg Asp Glu Asp Ala Gly Arg Tyr Trp Cys Thr Val Met Asp Gln
 100 105 110
 Asn His Lys Tyr Gln Asn Trp Arg Val Tyr Asp Val Ser Val Leu Lys
 115 120 125
 Gly Ser Gln Phe Ser Val Lys Ser Pro Asp Gly Pro Ser Cys Ala Ala
 130 135 140
 Leu Leu Cys Ser Val Val Pro Ala Arg Arg Leu Asp Ser Val Thr Trp
 145 150 155 160
 Leu Glu Gly Arg Asn Thr Val Arg Gly His Ala Gln Tyr Phe Trp Gly
 165 170 175
 Glu Gly Ala Ala Leu Leu Leu Val Cys Pro Thr Glu Gly Leu Pro Glu
 180 185 190

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Thr Arg Ala Arg Arg Pro Arg Asn Ile Arg Cys Leu Leu Pro Gln Asn
 195 200 205

Lys Arg Phe Ser Phe Ser Leu Ala Ala Ala Ser Ala Glu Pro Ser Pro
 210 215 220

Thr Val Cys Ala Thr Leu Pro Ser Trp Asp Val Pro
 225 230 235

<210> SEQ ID NO 21
 <211> LENGTH: 206
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 21

Met Ala Pro Ala Ala Ser Ala Cys Ala Gly Ala Pro Gly Ser His Pro
 1 5 10 15

Ala Thr Thr Ile Phe Val Cys Leu Phe Leu Ile Ile Tyr Cys Pro Asp
 20 25 30

Arg Ala Ser Ala Ile Gln Val Thr Val Pro Asp Pro Tyr His Val Val
 35 40 45

Ile Leu Phe Gln Pro Val Thr Leu His Cys Thr Tyr Gln Met Ser Asn
 50 55 60

Thr Leu Thr Ala Pro Ile Val Ile Trp Lys Tyr Lys Ser Phe Cys Arg
 65 70 75 80

Asp Arg Val Ala Asp Ala Phe Ser Pro Ala Ser Val Asp Asn Gln Leu
 85 90 95

Asn Ala Gln Leu Ala Ala Gly Asn Pro Gly Tyr Asn Pro Tyr Val Glu
 100 105 110

Cys Gln Asp Ser Val Arg Thr Val Arg Val Val Ala Thr Lys Gln Gly
 115 120 125

Asn Ala Val Thr Leu Gly Asp Tyr Tyr Gln Gly Arg Arg Ile Thr Ile
 130 135 140

Thr Gly Asn Ala Asp Leu Thr Phe Glu Gln Thr Ala Trp Gly Asp Ser
 145 150 155 160

Gly Val Tyr Tyr Cys Ser Val Val Ser Ala Gln Asp Leu Asp Gly Asn
 165 170 175

Asn Glu Ala Tyr Ala Glu Leu Ile Val Leu Gly Arg Thr Ser Glu Ala
 180 185 190

Pro Glu Leu Leu Pro Gly Phe Arg Ala Gly Pro Leu Glu Asp
 195 200 205

<210> SEQ ID NO 22
 <211> LENGTH: 192
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 22

Met Ala Leu Leu Ala Gly Gly Leu Ser Arg Gly Leu Gly Ser His Pro
 1 5 10 15

Ala Ala Ala Gly Arg Asp Ala Val Val Phe Val Trp Leu Leu Leu Ser
 20 25 30

Thr Trp Cys Thr Ala Pro Ala Arg Ala Ile Gln Val Thr Val Ser Asn
 35 40 45

Pro Tyr His Val Val Ile Leu Phe Gln Pro Val Thr Leu Pro Cys Thr
 50 55 60

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Tyr Gln Met Thr Ser Thr Pro Thr Gln Pro Ile Val Ile Trp Lys Tyr
65              70              75              80

Lys Ser Phe Cys Arg Asp Arg Ile Ala Asp Ala Phe Ser Pro Ala Ser
85              90              95

Val Asp Asn Gln Leu Asn Ala Gln Leu Ala Ala Gly Asn Pro Gly Tyr
100            105            110

Asn Pro Tyr Val Glu Cys Gln Asp Ser Val Arg Thr Val Arg Val Val
115            120            125

Ala Thr Lys Gln Gly Asn Ala Val Thr Leu Gly Asp Tyr Tyr Gln Gly
130            135            140

Arg Arg Ile Thr Ile Thr Gly Asn Ala Asp Leu Thr Phe Asp Gln Thr
145            150            155            160

Ala Trp Gly Asp Ser Gly Val Tyr Tyr Cys Ser Val Val Ser Ala Gln
165            170            175

Asp Leu Gln Gly Asn Asn Glu Ala Tyr Ala Glu Leu Ile Val Leu Asp
180            185            190

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<210> SEQ ID NO 23
<211> LENGTH: 451
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide

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<400> SEQUENCE: 23

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Asp Ser Ile Gln Thr Ile Tyr Val Ala Ser Gly Glu Ser Val Glu Met
1      5      10      15

Pro Cys Pro Ser Pro Pro Ser Leu Leu Gly Gly Gln Leu Leu Thr Trp
20     25     30

Phe Arg Ser Pro Val Ala Gly Ser Ser Thr Ile Leu Val Ala Gln Val
35     40     45

Gln Val Asp Lys Pro Val Ser Asp Leu Arg Lys Pro Glu Pro Asp Ser
50     55     60

Arg Tyr Lys Leu Phe Gly Asn Tyr Ser Leu Trp Leu Glu Gly Ser Arg
65     70     75     80

Asp Glu Asp Ala Gly Arg Tyr Trp Cys Thr Val Met Asp Gln Asn His
85     90     95

Lys Tyr Gln Asn Trp Arg Val Tyr Asp Val Ser Val Leu Lys Gly Ser
100    105    110

Gln Phe Ser Val Lys Ser Pro Asp Gly Pro Ser Cys Ala Ala Leu Leu
115    120    125

Cys Ser Val Val Pro Ala Arg Arg Leu Asp Ser Val Thr Trp Leu Glu
130    135    140

Gly Arg Asn Thr Val Arg Gly His Ala Gln Tyr Phe Trp Gly Glu Gly
145    150    155    160

Ala Ala Leu Leu Leu Val Cys Pro Thr Glu Gly Leu Pro Glu Thr Arg
165    170    175

Ala Arg Arg Pro Arg Asn Ile Arg Cys Leu Leu Pro Gln Asn Lys Arg
180    185    190

Phe Ser Phe Ser Leu Ala Ala Ala Ser Ala Glu Pro Ser Pro Thr Val
195    200    205

Cys Ala Thr Leu Pro Ser Trp Asp Val Pro Glu Pro Arg Gly Pro Thr
210    215    220

Ile Lys Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly
225    230    235    240

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[illegible]

<400> SEQUENCE: 24

Leu	Gln	Leu	Leu	Leu	Asn	Pro	Ser	Arg	Ala	Asn	Leu	Ser	Val	Arg	Pro	
1				5					10					15		
Asn	Ser	Glu	Val	Leu	Pro	Gly	Ile	His	Pro	Asp	Leu	Glu	Ala	Val	Ala	
			20					25					30			
Ile	Gly	Glu	Val	His	Asp	Asn	Val	Thr	Leu	Arg	Cys	Gly	Ser	Ala	Ser	
		35					40					45				
Gly	Ser	Arg	Gly	Leu	Val	Thr	Trp	Tyr	Arg	Asn	Asp	Ser	Glu	Pro	Ala	
	50					55					60					
Phe	Leu	Val	Ser	Phe	Asn	Ser	Ser	Leu	Pro	Pro	Ala	Ala	Pro	Arg	Phe	
65					70					75					80	
Ser	Leu	Glu	Asp	Ala	Gly	Ala	Leu	Arg	Ile	Glu	Ala	Leu	Arg	Leu	Glu	
				85					90					95		
Asp	Asp	Gly	Asn	Tyr	Thr	Cys	Gln	Glu	Val	Leu	Asn	Glu	Thr	His	Trp	
			100					105					110			
Phe	Pro	Val	Arg	Leu	Arg	Val	Ala	Ser	Gly	Pro	Ala	Tyr	Val	Glu	Val	
		115					120					125				
Asn	Ile	Ser	Ala	Thr	Gly	Thr	Leu	Pro	Asn	Gly	Thr	Leu	Tyr	Ala	Ala	
	130					135					140					

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Arg Gly Ser Gln Val Asp Phe Asn Cys Cys Ser Ala Ala Gln Pro Pro	145	150	155	160
Pro Glu Val Glu Trp Trp Ile Gln Thr His Ser Ile Pro Glu Phe Leu	165	170	175	
Gly Lys Asn Leu Ser Ala Asn Ser Phe Thr Leu Met Leu Met Ser Gln	180	185	190	
Asn Leu Gln Gly Asn Tyr Thr Cys Ser Ala Thr Asn Val Leu Ser Gly	195	200	205	
Arg Gln Arg Lys Val Thr Thr Glu Leu Leu Val Tyr Trp Pro Pro Pro	210	215	220	
Ser Ala Pro Gln Cys Ser Val Glu Val Ser Ser Glu Ser Thr Thr Leu	225	230	235	240
Glu Leu Ala Cys Asn Trp Asp Gly Gly Tyr Pro Asp Pro Thr Phe Leu	245	250	255	
Trp Thr Glu Glu Pro Gly Gly Thr Ile Met Gly Asn Ser Lys Leu Gln	260	265	270	
Thr Leu Ser Pro Ala Gln Leu Leu Glu Gly Lys Lys Phe Lys Cys Val	275	280	285	
Gly Asn His Ile Leu Gly Pro Glu Ser Gly Ala Ser Cys Val Val Lys	290	295	300	
Leu Ser Ser Pro Leu Leu Pro Ser Gln Pro Met Arg Thr Cys Phe Val	305	310	315	320
Gly Gly Asn Val Thr Leu Thr Cys Glu Val Ser Gly Ala Asn Pro Pro	325	330	335	
Ala Arg Ile Gln Trp Leu Arg Asn Leu Thr Gln Pro Ala Ile Gln Pro	340	345	350	
Ser Ser His Tyr Ile Ile Thr Gln Gln Gly Gln Ser Ser Ser Leu Thr	355	360	365	
Ile His Asn Cys Ser Gln Asp Leu Asp Glu Gly Phe Tyr Tyr Cys Gln	370	375	380	
Ala Glu Asn Leu Val Gly Val Arg Ala Thr Asn Ile Trp Leu Ser Val	385	390	395	400
Lys Glu Pro Leu Asn Ile Gly Gly Glu Pro Arg Gly Pro Thr Ile Lys	405	410	415	
Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly Pro	420	425	430	
Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser	435	440	445	
Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp	450	455	460	
Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr	465	470	475	480
Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val	485	490	495	
Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu	500	505	510	
Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Glu Arg	515	520	525	
Thr Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val	530	535	540	
Leu Pro Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr	545	550	555	560

Cys	Met	Val	Thr	Asp 565	Phe	Met	Pro	Glu	Asp 570	Ile	Tyr	Val	Glu	Trp 575	Thr
Asn	Asn	Gly	Lys 580	Thr	Glu	Leu	Asn	Tyr 585	Lys	Asn	Thr	Glu	Pro 590	Val	Leu
Asp	Ser	Asp	Gly 595	Ser	Tyr	Phe	Met 600	Tyr	Ser	Lys	Leu	Arg 605	Val	Glu	Lys
Lys	Asn	Trp	Val 610	Glu	Arg	Asn 615	Ser	Tyr	Ser	Cys 620	Ser	Val	Val	His	Glu
Gly 625	Leu	His	Asn	His 630	His	Thr	Thr	Lys	Ser	Phe 635	Ser	Arg	Thr	Pro	Gly 640
Lys															
<210> SEQ ID NO 25															
<211> LENGTH: 439															
<212> TYPE: PRT															
<213> ORGANISM: Artificial sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: Synthetic polypeptide															
<400> SEQUENCE: 25															
Glu 1	Leu	Ala	Pro 5	Gln	Ile	Asp	Gly	Gln	Thr 10	Trp	Ala	Glu	Arg 15	Ala	Leu
Arg	Glu	Asn	Glu 20	His	His	Ala	Phe	Thr 25	Cys	Arg	Val	Ala	Gly 30	Gly	Ser
Ala	Thr	Pro 35	Arg	Leu	Ala	Trp	Tyr 40	Leu	Asp	Gly	Gln 45	Leu	Gln	Glu	Ala
Thr	Thr 50	Ser	Arg	Leu	Leu 55	Ser	Val	Gly	Gly	Asp 60	Ala	Phe	Ser	Gly	Gly
Thr 65	Ser	Thr	Phe	Thr 70	Val	Thr	Ala	Gln	Arg 75	Ser	Gln	His	Glu	Leu	Asn 80
Cys	Ser	Leu	Gln 85	Asp	Pro	Gly	Ser	Gly	Arg 90	Pro	Ala	Asn	Ala 95	Ser	Val
Ile	Leu	Asn 100	Val	Gln	Phe	Lys	Pro	Glu 105	Ile	Ala	Gln	Val	Gly 110	Ala	Lys
Tyr	Gln	Glu 115	Ala	Gln	Gly	Pro	Gly 120	Leu	Leu	Val	Val	Leu 125	Phe	Ala	Leu
Val	Arg 130	Ala	Asn	Pro	Pro 135	Ala	Asn	Val	Thr	Trp	Ile 140	Asp	Gln	Asp	Gly
Pro 145	Val	Thr	Val	Asn 150	Ala	Ser	Asp	Phe	Leu	Val 155	Leu	Asp	Ala	Gln	Asn 160
Tyr	Pro	Trp	Leu 165	Thr	Asn	His	Thr	Val	Gln 170	Leu	Gln	Leu	Arg	Ser 175	Leu
Ala	His	Asn 180	Leu	Ser	Val	Val	Ala	Thr 185	Asn	Asp	Val	Gly 190	Val	Thr	Ser
Ala	Ser	Leu 195	Pro	Ala	Pro	Gly	Leu 200	Leu	Ala	Thr	Arg	Ile 205	Glu	Glu	Pro
Arg	Gly 210	Pro	Thr	Ile	Lys 215	Pro	Cys	Pro	Pro	Cys 220	Lys	Cys	Pro	Ala	Pro
Asn 225	Leu	Leu	Gly	Gly 230	Pro	Ser	Val	Phe	Ile	Phe 235	Pro	Pro	Lys	Ile	Lys 240
Asp	Val	Leu	Met 245	Ile	Ser	Leu	Ser	Pro	Ile 250	Val	Thr	Cys	Val	Val	Val
Asp	Val	Ser	Glu 260	Asp	Asp	Pro	Asp	Val 265	Gln	Ile	Ser	Trp	Phe	Val	Asn
Asn	Val	Glu	Val	His	Thr	Ala	Gln	Thr	Gln	Thr	His	Arg	Glu	Asp	Tyr

-continued

275	280	285
Asn Ser Thr Leu Arg Val	Val Ser Ala Leu Pro	Ile Gln His Gln Asp
290	295	300
Trp Met Ser Gly Lys Glu	Phe Lys Cys Lys Val	Asn Asn Lys Asp Leu
305	310	315
Pro Ala Pro Ile Glu Arg Thr	Ile Ser Lys Pro Lys	Gly Ser Val Arg
325	330	335
Ala Pro Gln Val Tyr Val	Leu Pro Pro Pro Glu	Glu Glu Met Thr Lys
340	345	350
Lys Gln Val Thr Leu Thr	Cys Met Val Thr Asp	Phe Met Pro Glu Asp
355	360	365
Ile Tyr Val Glu Trp Thr	Asn Asn Gly Lys Thr	Glu Leu Asn Tyr Lys
370	375	380
Asn Thr Glu Pro Val Leu	Asp Ser Asp Gly Ser	Tyr Phe Met Tyr Ser
385	390	395
Lys Leu Arg Val Glu Lys	Lys Asn Trp Val Glu	Arg Asn Ser Tyr Ser
405	410	415
Cys Ser Val Val His Glu	Gly Leu His Asn His	His Thr Thr Lys Ser
420	425	430
Phe Ser Arg Thr Pro Gly	Lys	
435		
<210> SEQ ID NO 26		
<211> LENGTH: 403		
<212> TYPE: PRT		
<213> ORGANISM: Artificial sequence		
<220> FEATURE:		
<223> OTHER INFORMATION: Synthetic polypeptide		
<400> SEQUENCE: 26		
Ile Gln Val Thr Val Pro	Asp Pro Tyr His Val Val	Ile Leu Phe Gln
1	5	10
Pro Val Thr Leu His Cys	Thr Tyr Gln Met Ser Asn	Thr Leu Thr Ala
20	25	30
Pro Ile Val Ile Trp Lys	Tyr Lys Ser Phe Cys Arg	Asp Arg Val Ala
35	40	45
Asp Ala Phe Ser Pro Ala	Ser Val Asp Asn Gln Leu	Asn Ala Gln Leu
50	55	60
Ala Ala Gly Asn Pro Gly	Tyr Asn Pro Tyr Val	Glu Cys Gln Asp Ser
65	70	75
Val Arg Thr Val Arg Val	Val Ala Thr Lys Gln	Gly Asn Ala Val Thr
85	90	95
Leu Gly Asp Tyr Tyr Gln	Gly Arg Arg Ile Thr	Ile Thr Gly Asn Ala
100	105	110
Asp Leu Thr Phe Glu Gln	Thr Ala Trp Gly Asp Ser	Gly Val Tyr Tyr
115	120	125
Cys Ser Val Val Ser Ala	Gln Asp Leu Asp Gly	Asn Asn Glu Ala Tyr
130	135	140
Ala Glu Leu Ile Val Leu	Gly Arg Thr Ser Glu	Ala Pro Glu Leu Leu
145	150	155
Pro Gly Phe Arg Ala Gly	Pro Leu Glu Asp Glu	Pro Arg Gly Pro Thr
165	170	175
Ile Lys Pro Cys Pro Pro	Cys Lys Cys Pro Ala	Pro Asn Leu Leu Gly
180	185	190
Gly Pro Ser Val Phe Ile	Phe Pro Pro Lys Ile	Lys Asp Val Leu Met

-continued

195					200					205					
Ile	Ser	Leu	Ser	Pro	Ile	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Glu
210					215					220					
Asp	Asp	Pro	Asp	Val	Gln	Ile	Ser	Trp	Phe	Val	Asn	Asn	Val	Glu	Val
225					230					235					240
His	Thr	Ala	Gln	Thr	Gln	Thr	His	Arg	Glu	Asp	Tyr	Asn	Ser	Thr	Leu
				245					250					255	
Arg	Val	Val	Ser	Ala	Leu	Pro	Ile	Gln	His	Gln	Asp	Trp	Met	Ser	Gly
			260					265					270		
Lys	Glu	Phe	Lys	Cys	Lys	Val	Asn	Asn	Lys	Asp	Leu	Pro	Ala	Pro	Ile
		275					280					285			
Glu	Arg	Thr	Ile	Ser	Lys	Pro	Lys	Gly	Ser	Val	Arg	Ala	Pro	Gln	Val
	290					295					300				
Tyr	Val	Leu	Pro	Pro	Pro	Glu	Glu	Glu	Met	Thr	Lys	Lys	Gln	Val	Thr
305					310					315					320
Leu	Thr	Cys	Met	Val	Thr	Asp	Phe	Met	Pro	Glu	Asp	Ile	Tyr	Val	Glu
			325					330						335	
Trp	Thr	Asn	Asn	Gly	Lys	Thr	Glu	Leu	Asn	Tyr	Lys	Asn	Thr	Glu	Pro
			340					345					350		
Val	Leu	Asp	Ser	Asp	Gly	Ser	Tyr	Phe	Met	Tyr	Ser	Lys	Leu	Arg	Val
		355					360					365			
Glu	Lys	Lys	Asn	Trp	Val	Glu	Arg	Asn	Ser	Tyr	Ser	Cys	Ser	Val	Val
	370					375					380				
His	Glu	Gly	Leu	His	Asn	His	His	Thr	Thr	Lys	Ser	Phe	Ser	Arg	Thr
385					390					395					400
Pro Gly Lys															

<210> SEQ ID NO 27

<211> LENGTH: 233

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 27

Glu	Pro	Arg	Gly	Pro	Thr	Ile	Lys	Pro	Cys	Pro	Pro	Cys	Lys	Cys	Pro
1				5				10					15		
Ala	Pro	Asn	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Lys
		20					25						30		
Ile	Lys	Asp	Val	Leu	Met	Ile	Ser	Leu	Ser	Pro	Ile	Val	Thr	Cys	Val
	35					40						45			
Val	Val	Asp	Val	Ser	Glu	Asp	Asp	Pro	Asp	Val	Gln	Ile	Ser	Trp	Phe
	50					55					60				
Val	Asn	Asn	Val	Glu	Val	His	Thr	Ala	Gln	Thr	Gln	Thr	His	Arg	Glu
65					70					75					80
Asp	Tyr	Asn	Ser	Thr	Leu	Arg	Val	Val	Ser	Ala	Leu	Pro	Ile	Gln	His
			85					90						95	
Gln	Asp	Trp	Met	Ser	Gly	Lys	Glu	Phe	Lys	Cys	Lys	Val	Asn	Asn	Lys
			100					105					110		
Asp	Leu	Pro	Ala	Pro	Ile	Glu	Arg	Thr	Ile	Ser	Lys	Pro	Lys	Gly	Ser
		115					120					125			
Val	Arg	Ala	Pro	Gln	Val	Tyr	Val	Leu	Pro	Pro	Pro	Glu	Glu	Glu	Met
	130					135						140			
Thr	Lys	Lys	Gln	Val	Thr	Leu	Thr	Cys	Met	Val	Thr	Asp	Phe	Met	Pro
145					150					155					160

[illegible]

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<210> SEQ ID NO 28
<211> LENGTH: 365
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide
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<400> SEQUENCE: 28

Met 1	Glu	Leu	Pro	Leu 5	Ser	Gln	Ala	Thr	Leu 10	Arg	His	Thr	Leu	Leu 15	Leu
Leu	Pro	Ala	Leu 20	Leu	Ser	Ser	Gly	Gln 25	Gly	Glu	Leu	Ala	Pro 30	Gln	Ile
Asp	Gly	Gln	Thr 35	Trp	Ala	Glu	Arg 40	Ala	Leu	Arg	Glu	Asn 45	Glu	His	His
Ala	Phe 50	Thr	Cys	Arg	Val 55	Ala	Gly	Gly	Ser	Ala	Thr 60	Pro	Arg	Leu	Ala
Trp 65	Tyr	Leu	Asp	Gly 70	Gln	Leu	Gln	Glu	Ala	Thr 75	Thr	Ser	Arg	Leu	Leu 80
Ser	Val	Gly	Gly 85	Asp	Ala	Phe	Ser	Gly	Gly 90	Thr	Ser	Thr	Phe	Thr 95	Val
Thr	Ala	Gln	Arg 100	Ser	Gln	His	Glu	Leu 105	Asn	Cys	Ser	Leu	Gln 110	Asp	Pro
Gly	Ser	Gly 115	Arg	Pro	Ala	Asn	Ala 120	Ser	Val	Ile	Leu	Asn 125	Val	Gln	Phe
Lys 130	Pro	Glu	Ile	Ala	Gln 135	Val	Gly	Ala	Lys	Tyr	Gln 140	Glu	Ala	Gln	Gly
Pro 145	Gly	Leu	Leu	Val 150	Val	Leu	Phe	Ala	Leu	Val 155	Arg	Ala	Asn	Pro	Pro 160
Ala	Asn	Val	Thr 165	Trp	Ile	Asp	Gln	Asp	Gly 170	Pro	Val	Thr	Val	Asn 175	Ala
Ser	Asp	Phe 180	Leu	Val	Leu	Asp	Ala	Gln 185	Asn	Tyr	Pro	Trp	Leu 190	Thr	Asn
His	Thr 195	Val	Gln	Leu	Gln	Leu	Arg 200	Ser	Leu	Ala	His	Asn 205	Leu	Ser	Val
Val 210	Ala	Thr	Asn	Asp	Val	Gly 215	Val	Thr	Ser	Ala	Ser 220	Leu	Pro	Ala	Pro
Gly 225	Leu	Leu	Ala	Thr 230	Arg	Ile	Glu	Val	Pro	Leu 235	Leu	Gly	Ile	Val	Val 240
Ala	Gly	Gly	Leu 245	Ala	Leu	Gly	Thr	Leu	Val 250	Gly	Phe	Ser	Thr	Leu 255	Val
Ala	Cys	Leu 260	Val	Cys	Arg	Lys	Glu	Lys 265	Lys	Thr	Lys	Gly	Pro 270	Ser	Arg
Arg	Pro 275	Ser	Leu	Ile	Ser	Ser	Asp 280	Ser	Asn	Asn	Leu	Lys 285	Leu	Asn	Asn

-continued

Val Arg Leu Pro Arg Glu Asn Met Ser Leu Pro Ser Asn Leu Gln Leu
 290 295 300

Asn Asp Leu Thr Pro Asp Leu Arg Gly Lys Ala Thr Glu Arg Pro Met
 305 310 315 320

Ala Gln His Ser Ser Arg Pro Glu Leu Leu Glu Ala Glu Pro Gly Gly
 325 330 335

Leu Leu Thr Ser Arg Gly Phe Ile Arg Leu Pro Met Leu Gly Tyr Ile
 340 345 350

Tyr Arg Val Ser Ser Val Ser Ser Asp Glu Ile Trp Leu
 355 360 365

<210> SEQ ID NO 29
 <211> LENGTH: 300
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 29

Met Ala Val Val Val Phe Leu Leu Phe Leu Cys Gly His Ser Gln Ala
 1 5 10 15

Val Ala Asp Ser Ile Gln Thr Ile Tyr Val Ala Ser Gly Glu Ser Val
 20 25 30

Glu Met Pro Cys Pro Ser Pro Pro Ser Leu Leu Gly Gly Gln Leu Leu
 35 40 45

Thr Trp Phe Arg Ser Pro Val Ala Gly Ser Ser Thr Ile Leu Val Ala
 50 55 60

Gln Val Gln Val Asp Lys Pro Val Ser Asp Leu Arg Lys Pro Glu Pro
 65 70 75 80

Asp Ser Arg Tyr Lys Leu Phe Gly Asn Tyr Ser Leu Trp Leu Glu Gly
 85 90 95

Ser Arg Asp Glu Asp Ala Gly Arg Tyr Trp Cys Thr Val Met Asp Gln
 100 105 110

Asn His Lys Tyr Gln Asn Trp Arg Val Tyr Asp Val Ser Val Leu Lys
 115 120 125

Gly Ser Gln Phe Ser Val Lys Ser Pro Asp Gly Pro Ser Cys Ala Ala
 130 135 140

Leu Leu Cys Ser Val Val Pro Ala Arg Arg Leu Asp Ser Val Thr Trp
 145 150 155 160

Leu Glu Gly Arg Asn Thr Val Arg Gly His Ala Gln Tyr Phe Trp Gly
 165 170 175

Glu Gly Ala Ala Leu Leu Leu Val Cys Pro Thr Glu Gly Leu Pro Glu
 180 185 190

Thr Arg Ala Arg Arg Pro Arg Asn Ile Arg Cys Leu Leu Pro Gln Asn
 195 200 205

Lys Arg Phe Ser Phe Ser Leu Ala Ala Ala Ser Ala Glu Pro Ser Pro
 210 215 220

Thr Val Cys Ala Thr Leu Pro Ser Trp Asp Val Pro Trp Ile Leu Val
 225 230 235 240

Leu Leu Phe Thr Ala Gly Gln Gly Val Thr Ile Ile Ala Leu Ser Ile
 245 250 255

Val Leu Trp Arg Arg Arg Arg Ala Gln Gly Ser Arg Asp Arg Glu Pro
 260 265 270

Ser Val Pro His Phe Lys Pro Glu Val Gln Val Tyr Glu Asn Ile His
 275 280 285

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Leu Ala Arg Leu Ser Pro Pro Asn His Lys Thr Arg
 290 295 300

<210> SEQ ID NO 30
 <211> LENGTH: 558
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 30

Met Ala Gly Leu Arg Val Leu Leu Cys Leu Gly Ala Leu Leu Ala Arg
 1 5 10 15
 Gln Gly Ser Ala Gly Leu Gln Leu Leu Asn Pro Ser Arg Ala Asn
 20 25 30
 Leu Ser Val Arg Pro Asn Ser Glu Val Leu Pro Gly Ile His Pro Asp
 35 40 45
 Leu Glu Ala Val Ala Ile Gly Glu Val His Asp Asn Val Thr Leu Arg
 50 55 60
 Cys Gly Ser Ala Ser Gly Ser Arg Gly Leu Val Thr Trp Tyr Arg Asn
 65 70 75 80
 Asp Ser Glu Pro Ala Phe Leu Val Ser Phe Asn Ser Ser Leu Pro Pro
 85 90 95
 Ala Ala Pro Arg Phe Ser Leu Glu Asp Ala Gly Ala Leu Arg Ile Glu
 100 105 110
 Ala Leu Arg Leu Glu Asp Asp Gly Asn Tyr Thr Cys Gln Glu Val Leu
 115 120 125
 Asn Glu Thr His Trp Phe Pro Val Arg Leu Arg Val Ala Ser Gly Pro
 130 135 140
 Ala Tyr Val Glu Val Asn Ile Ser Ala Thr Gly Thr Leu Pro Asn Gly
 145 150 155 160
 Thr Leu Tyr Ala Ala Arg Gly Ser Gln Val Asp Phe Asn Cys Cys Ser
 165 170 175
 Ala Ala Gln Pro Pro Pro Glu Val Glu Trp Trp Ile Gln Thr His Ser
 180 185 190
 Ile Pro Glu Phe Leu Gly Lys Asn Leu Ser Ala Asn Ser Phe Thr Leu
 195 200 205
 Met Leu Met Ser Gln Asn Leu Gln Gly Asn Tyr Thr Cys Ser Ala Thr
 210 215 220
 Asn Val Leu Ser Gly Arg Gln Arg Lys Val Thr Thr Glu Leu Leu Val
 225 230 235 240
 Tyr Trp Pro Pro Pro Ser Ala Pro Gln Cys Ser Val Glu Val Ser Ser
 245 250 255
 Glu Ser Thr Thr Leu Glu Leu Ala Cys Asn Trp Asp Gly Gly Tyr Pro
 260 265 270
 Asp Pro Thr Phe Leu Trp Thr Glu Glu Pro Gly Gly Thr Ile Met Gly
 275 280 285
 Asn Ser Lys Leu Gln Thr Leu Ser Pro Ala Gln Leu Leu Glu Gly Lys
 290 295 300
 Lys Phe Lys Cys Val Gly Asn His Ile Leu Gly Pro Glu Ser Gly Ala
 305 310 315 320
 Ser Cys Val Val Lys Leu Ser Ser Pro Leu Leu Pro Ser Gln Pro Met
 325 330 335
 Arg Thr Cys Phe Val Gly Gly Asn Val Thr Leu Thr Cys Glu Val Ser
 340 345 350

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Gly Ala Asn Pro Pro Ala Arg Ile Gln Trp Leu Arg Asn Leu Thr Gln
 355 360 365
 Pro Ala Ile Gln Pro Ser Ser His Tyr Ile Ile Thr Gln Gln Gly Gln
 370 375 380
 Ser Ser Ser Leu Thr Ile His Asn Cys Ser Gln Asp Leu Asp Glu Gly
 385 390 395 400
 Phe Tyr Tyr Cys Gln Ala Glu Asn Leu Val Gly Val Arg Ala Thr Asn
 405 410 415
 Ile Trp Leu Ser Val Lys Glu Pro Leu Asn Ile Gly Gly Ile Val Gly
 420 425 430
 Thr Val Val Ser Leu Leu Leu Leu Gly Leu Ala Val Val Ser Gly Leu
 435 440 445
 Thr Leu Tyr Tyr Ser Pro Ala Phe Trp Trp Lys Gly Gly Ser Thr Phe
 450 455 460
 Arg Gly Gln Asp Met Gly Asp Val Met Val Leu Val Asp Ser Glu Glu
 465 470 475 480
 Glu Glu Glu Glu Glu Glu Glu Glu Glu Lys Glu Asp Val Ala Glu
 485 490 495
 Glu Val Glu Gln Glu Thr Asn Glu Thr Glu Glu Leu Pro Lys Gly Ile
 500 505 510
 Ser Lys His Gly His Ile His Arg Val Thr Ala Leu Val Asn Gly Asn
 515 520 525
 Leu Asp Arg Met Gly Asn Gly Phe Gln Glu Phe Gln Asp Asp Ser Asp
 530 535 540
 Gly Gln Gln Ser Gly Ile Val Gln Glu Asp Gly Lys Pro Val
 545 550 555

<210> SEQ ID NO 31
 <211> LENGTH: 594
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 31

Met Ala Pro Ala Ala Ser Ala Cys Ala Gly Ala Pro Gly Ser His Pro
 1 5 10 15
 Ala Thr Thr Ile Phe Val Cys Leu Phe Leu Ile Ile Tyr Cys Pro Asp
 20 25 30
 Arg Ala Ser Ala Ile Gln Val Thr Val Pro Asp Pro Tyr His Val Val
 35 40 45
 Ile Leu Phe Gln Pro Val Thr Leu His Cys Thr Tyr Gln Met Ser Asn
 50 55 60
 Thr Leu Thr Ala Pro Ile Val Ile Trp Lys Tyr Lys Ser Phe Cys Arg
 65 70 75 80
 Asp Arg Val Ala Asp Ala Phe Ser Pro Ala Ser Val Asp Asn Gln Leu
 85 90 95
 Asn Ala Gln Leu Ala Ala Gly Asn Pro Gly Tyr Asn Pro Tyr Val Glu
 100 105 110
 Cys Gln Asp Ser Val Arg Thr Val Arg Val Val Ala Thr Lys Gln Gly
 115 120 125
 Asn Ala Val Thr Leu Gly Asp Tyr Tyr Gln Gly Arg Arg Ile Thr Ile
 130 135 140
 Thr Gly Asn Ala Asp Leu Thr Phe Glu Gln Thr Ala Trp Gly Asp Ser
 145 150 155 160

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Gly	Val	Tyr	Tyr	Cys	Ser	Val	Val	Ser	Ala	Gln	Asp	Leu	Asp	Gly	Asn	
				165					170					175		
Asn	Glu	Ala	Tyr	Ala	Glu	Leu	Ile	Val	Leu	Gly	Arg	Thr	Ser	Glu	Ala	
		180						185					190			
Pro	Glu	Leu	Leu	Pro	Gly	Phe	Arg	Ala	Gly	Pro	Leu	Glu	Asp	Trp	Leu	
		195					200					205				
Phe	Val	Val	Val	Val	Cys	Leu	Ala	Ser	Leu	Leu	Phe	Phe	Leu	Leu	Leu	
	210					215					220					
Gly	Ile	Cys	Trp	Cys	Gln	Cys	Cys	Pro	His	Thr	Cys	Cys	Cys	Tyr	Val	
225					230					235					240	
Arg	Cys	Pro	Cys	Cys	Pro	Asp	Lys	Cys	Cys	Cys	Pro	Glu	Ala	Leu	Tyr	
			245					250						255		
Ala	Ala	Gly	Lys	Ala	Ala	Thr	Ser	Gly	Val	Pro	Ser	Ile	Tyr	Ala	Pro	
		260						265					270			
Ser	Ile	Tyr	Thr	His	Leu	Ser	Pro	Ala	Lys	Thr	Pro	Pro	Pro	Pro	Pro	
	275						280					285				
Ala	Met	Ile	Pro	Met	Arg	Pro	Pro	Tyr	Gly	Tyr	Pro	Gly	Asp	Phe	Asp	
	290					295					300					
Arg	Thr	Ser	Ser	Val	Gly	Gly	His	Ser	Ser	Gln	Val	Pro	Leu	Leu	Arg	
305					310					315					320	
Glu	Val	Asp	Gly	Ser	Val	Ser	Ser	Glu	Val	Arg	Ser	Gly	Tyr	Arg	Ile	
			325					330					335			
Gln	Ala	Asn	Gln	Gln	Asp	Asp	Ser	Met	Arg	Val	Leu	Tyr	Tyr	Met	Glu	
		340						345					350			
Lys	Glu	Leu	Ala	Asn	Phe	Asp	Pro	Ser	Arg	Pro	Gly	Pro	Pro	Asn	Gly	
	355						360				365					
Arg	Val	Glu	Arg	Ala	Met	Ser	Glu	Val	Thr	Ser	Leu	His	Glu	Asp	Asp	
	370					375					380					
Trp	Arg	Ser	Arg	Pro	Ser	Arg	Ala	Pro	Ala	Leu	Thr	Pro	Ile	Arg	Asp	
385				390					395						400	
Glu	Glu	Trp	Asn	Arg	His	Ser	Pro	Arg	Ser	Pro	Arg	Thr	Trp	Glu	Gln	
			405					410					415			
Glu	Pro	Leu	Gln	Glu	Gln	Pro	Arg	Gly	Gly	Trp	Gly	Ser	Gly	Arg	Pro	
		420						425				430				
Arg	Ala	Arg	Ser	Val	Asp	Ala	Leu	Asp	Asp	Ile	Asn	Arg	Pro	Gly	Ser	
	435					440					445					
Thr	Glu	Ser	Gly	Arg	Ser	Ser	Pro	Pro	Ser	Ser	Gly	Arg	Arg	Gly	Arg	
	450				455						460					
Ala	Tyr	Ala	Pro	Pro	Arg	Ser	Arg	Ser	Arg	Asp	Asp	Leu	Tyr	Asp	Pro	
465					470				475					480		
Asp	Asp	Pro	Arg	Asp	Leu	Pro	His	Ser	Arg	Asp	Pro	His	Tyr	Tyr	Asp	
			485					490					495			
Asp	Leu	Arg	Ser	Arg	Asp	Pro	Arg	Ala	Asp	Pro	Arg	Ser	Arg	Gln	Arg	
		500						505				510				
Ser	His	Asp	Pro	Arg	Asp	Ala	Gly	Phe	Arg	Ser	Arg	Asp	Pro	Gln	Tyr	
	515					520						525				
Asp	Gly	Arg	Leu	Leu	Glu	Glu	Ala	Leu	Lys	Lys	Lys	Gly	Ala	Gly	Glu	
	530				535						540					
Arg	Arg	Arg	Val	Tyr	Arg	Glu	Glu	Glu	Glu	Glu	Glu	Glu	Gly	His		
545					550				555					560		
Tyr	Pro	Pro	Ala	Pro	Pro	Pro	Tyr	Ser	Glu	Thr	Asp	Ser	Gln	Ala	Ser	
			565					570					575			

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Arg Glu Arg Arg Met Lys Lys Asn Leu Ala Leu Ser Arg Glu Ser Leu
580 585 590

Val Val

<210> SEQ ID NO 32

<211> LENGTH: 575

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 32

Met Ala Pro Ala Ala Ser Ala Cys Ala Gly Ala Pro Gly Ser His Pro
1 5 10 15

Ala Thr Thr Ile Phe Val Cys Leu Phe Leu Ile Ile Tyr Cys Pro Asp
20 25 30

Arg Ala Ser Ala Ile Gln Val Thr Val Pro Asp Pro Tyr His Val Val
35 40 45

Ile Leu Phe Gln Pro Val Thr Leu His Cys Thr Tyr Gln Met Ser Asn
50 55 60

Thr Leu Thr Ala Pro Ile Val Ile Trp Lys Tyr Lys Ser Phe Cys Arg
65 70 75 80

Asp Arg Val Ala Asp Ala Phe Ser Pro Ala Ser Val Asp Asn Gln Leu
85 90 95

Asn Ala Gln Leu Ala Ala Gly Asn Pro Gly Tyr Asn Pro Tyr Val Glu
100 105 110

Cys Gln Asp Ser Val Arg Thr Val Arg Val Val Ala Thr Lys Gln Gly
115 120 125

Asn Ala Val Thr Leu Gly Asp Tyr Tyr Gln Gly Arg Arg Ile Thr Ile
130 135 140

Thr Gly Asn Ala Asp Leu Thr Phe Glu Gln Thr Ala Trp Gly Asp Ser
145 150 155 160

Gly Val Tyr Tyr Cys Ser Val Val Ser Ala Gln Asp Leu Asp Gly Asn
165 170 175

Asn Glu Ala Tyr Ala Glu Leu Ile Val Leu Asp Trp Leu Phe Val Val
180 185 190

Val Val Cys Leu Ala Ser Leu Leu Phe Phe Leu Leu Leu Gly Ile Cys
195 200 205

Trp Cys Gln Cys Cys Pro His Thr Cys Cys Cys Tyr Val Arg Cys Pro
210 215 220

Cys Cys Pro Asp Lys Cys Cys Cys Pro Glu Ala Leu Tyr Ala Ala Gly
225 230 235 240

Lys Ala Ala Thr Ser Gly Val Pro Ser Ile Tyr Ala Pro Ser Ile Tyr
245 250 255

Thr His Leu Ser Pro Ala Lys Thr Pro Pro Pro Pro Pro Ala Met Ile
260 265 270

Pro Met Arg Pro Pro Tyr Gly Tyr Pro Gly Asp Phe Asp Arg Thr Ser
275 280 285

Ser Val Gly Gly His Ser Ser Gln Val Pro Leu Leu Arg Glu Val Asp
290 295 300

Gly Ser Val Ser Ser Glu Val Arg Ser Gly Tyr Arg Ile Gln Ala Asn
305 310 315 320

Gln Gln Asp Asp Ser Met Arg Val Leu Tyr Tyr Met Glu Lys Glu Leu
325 330 335

Ala Asn Phe Asp Pro Ser Arg Pro Gly Pro Pro Asn Gly Arg Val Glu

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340	345	350
Arg Ala Met Ser Glu Val Thr Ser Leu His Glu Asp Asp Trp Arg Ser 355 360 365		
Arg Pro Ser Arg Ala Pro Ala Leu Thr Pro Ile Arg Asp Glu Glu Trp 370 375 380		
Asn Arg His Ser Pro Arg Ser Pro Arg Thr Trp Glu Gln Glu Pro Leu 385 390 395 400		
Gln Glu Gln Pro Arg Gly Gly Trp Gly Ser Gly Arg Pro Arg Ala Arg 405 410 415		
Ser Val Asp Ala Leu Asp Asp Ile Asn Arg Pro Gly Ser Thr Glu Ser 420 425 430		
Gly Arg Ser Ser Pro Pro Ser Ser Gly Arg Arg Gly Arg Ala Tyr Ala 435 440 445		
Pro Pro Arg Ser Arg Ser Arg Asp Asp Leu Tyr Asp Pro Asp Asp Pro 450 455 460		
Arg Asp Leu Pro His Ser Arg Asp Pro His Tyr Tyr Asp Asp Leu Arg 465 470 475 480		
Ser Arg Asp Pro Arg Ala Asp Pro Arg Ser Arg Gln Arg Ser His Asp 485 490 495		
Pro Arg Asp Ala Gly Phe Arg Ser Arg Asp Pro Gln Tyr Asp Gly Arg 500 505 510		
Leu Leu Glu Glu Ala Leu Lys Lys Lys Gly Ala Gly Glu Arg Arg Arg 515 520 525		
Val Tyr Arg Glu Glu Glu Glu Glu Glu Glu Gly His Tyr Pro Pro 530 535 540		
Ala Pro Pro Pro Tyr Ser Glu Thr Asp Ser Gln Ala Ser Arg Glu Arg 545 550 555 560		
Arg Met Lys Lys Asn Leu Ala Leu Ser Arg Glu Ser Leu Val Val 565 570 575		

<210> SEQ ID NO 33

<211> LENGTH: 654

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 33

```

gcagacaaca tgcaggccat ctatgtggcc ttgggggagg cagtagagct gccatgtccc      60
tcaccaccta ctctacatgg ggacgaacac ctgtcatggt tctgcagccc tgcagcaggc      120
tccttcacca ccttggtagc ccaagtccaa gtgggcaggc cagccccaga ccttgaaaaa      180
ccaggaaggg aatccaggct cagactgctg gggaactatt ctttgtggtt ggagggatcc      240
aaagaggaag atgccgggcg gtactggtgc gctgtgctag gtcagcacca caactaccag      300
aactggaggg tgtacgacgt cttggtgctc aaaggatccc agttatctgc aagggtgca      360
gatggatccc cctgcaatgt cctcctgtgc tctgtggtcc ccagcagacg catggactct      420
gtgacctggc aggaagggaa ggggtccgtg aggggccgtg ttcagtcctt ctggggcagt      480
gaggctgccc tgctcttggg gtgtcctggg gaggggcttt ctgagcccag gagccgaaga      540
ccaagaatca tccgctgcct catgactcac aacaaagggg tcagctttag cctggcagcc      600
tccatcgatg cttctctgc cctctgtgcc ccttcacagg gctgggacat gcct      654

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<210> SEQ ID NO 34

<211> LENGTH: 1149

-continued

<212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 34

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gttgtcattg gagaagtcca tgagaatggt actctgcact gtggcaacat ctcgggactg      60
aggggccagg tgacctggta ccggaacaac tcggagcctg tcttccttct ctcgccaac      120
tctagcctcc ggccagctga gcctcgttcc tctctagtgg atgccacctc cctgcacatt      180
gaatcgctga gcctgggaga tgagggaatc tacacctgcc aggagatcct gaatgtgact      240
cagtgggtcc aagtgtggct gcagggtggc agcgcccctc atcagattga ggteccacac      300
gtggccaccg gcacactccc caacggcacc ctctatgcag ccaggggctc ccaggtggac      360
ttcagctgca acagcagctc caggccacca cccgtgggtg aatgggtggt ccaggccctg      420
aattccagca gcgagtcctt tggccacaac ctgacagtca actttttctc actgttactg      480
atatcgccaa acctccaagg gaactacacc tgtttagcct tgaatcagct cagcaagaga      540
catcgaaagg tgaccaccga gctcctggtc tactatcccc ctccatcagc tccccagtgc      600
tgggcacaga tggcatcagg atcggttcctg ttgcagctta cctgtcgtg ggatggggga      660
tacctgacc ctgacttcct gtggatagaa gagccaggag gtgtaatcgt ggggaagtca      720
aagctggggg tggaaatgct gagcgagtcc cagctgtcgg atggcaagaa gttcaagtgt      780
gttacaagcc acatagtgtg gccagagtcg ggcgccagct gcattggtga gatcaggggt      840
ccctcccttc tctctgagcc catgaagact tgcttcactg ggggcaatgt gacgcttaca      900
tgccagggtg ctggggccta cccccctgcc aagatcctgt ggctgaggaa ccttaccag      960
cccaggtga tcatccagcc tagcagccgc catctcatta cccaggatgg ccagaactcc     1020
accctcacta tccacaactg ctcccaggac ctggatgagg gctactacat ctgccgagct     1080
gacagccctg taggggtgag ggagatggaa atctggctga gtgtgaaaga acctttaaat     1140
atcgggggg                                     1149

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<210> SEQ ID NO 35
 <211> LENGTH: 1320
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 35

```

atggccgcag gcggcagtgc gcccagagccc cgcgtcctcg tctgcctcgg ggcgctcctg      60
gccggctggg tcgccgtagg attggaggct gttgtcattg gagaagtcca tgagaatggt      120
actctgcact gtggcaacat ctcgggactg aggggccagg tgacctggta ccggaacaac      180
tcggagcctg tcttccttct ctcgccaac tctagcctcc ggccagctga gcctcgttcc      240
tctctagtgg atgccacctc cctgcacatt gaatcgctga gcctgggaga tgagggaatc      300
tacacctgcc aggagatcct gaatgtgact cagtgggtcc aagtgtggct gcagggtggc      360
aatccccctc catcagctcc ccagtgtctg gcacagatgg catcaggatc gttcatgttg      420
cagcttacct gtcgtgggga tgggggatac cctgacctg acttcctgtg gatagaagag      480
ccaggaggtg taatcgtggg gaagtcaaag ctgggggtgg aaatgctgag cgagtcccag      540
ctgtcgatg gcaagaagtt caagtgtgtt acaagccaca tagttgggcc agagtcgggc      600
gccagctgca tgggtgcagat caggggtccc tcccttctct ctgagcccat gaagacttgc      660

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ttcactgggg gcaatgtgac gcttacatgc caggtgtctg gggcctaccc cctgccaag	720
atcctgtggc tgaggaacct taccagccc gaggtgatca tccagcctag cagccgccat	780
ctcattaccc aggatggcca gaactccacc ctcactatcc acaactgctc ccaggacctg	840
gatgagggct actacatctg ccgagctgac agccctgtag gggtagggga gatggaaatc	900
tggctgagtg tgaaagaacc tttaaataac ggggggattg tgggaacctat tgtgagcctc	960
cttctgctgg gactggccat tatctcaggg cttctgttgc attatagccc tgtgttctgc	1020
tggaaagtag gaaacacttc caggggacaa aacatggatg atgtcatggg ttggtggat	1080
tcagaagagg aagaggagga ggaggaggag gagggaggaag atgctgcagt aggggaacag	1140
gaggggagcac gtgagagaga ggagttgccaa aaagaaatac ctaagcagga ccacattcac	1200
agagtgaccg ccttggtgaa tgggaacata gaacagatgg gaaatggatt ccaggatctt	1260
caagatgaca gcagtggaga gcaaatgac attgttcaag aagaagacag gccagtctga	1320

<210> SEQ ID NO 36

<211> LENGTH: 846

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 36

gttgtcattg gagaagtcca tgagaatgtt actctgcact gtggcaacat ctggggactg	60
agggggccagg tgacctggta ccggaacaac tcggagcctg tcttccttct ctgtccaac	120
tctagcctcc ggccagctga gcctcgcttc tctctagtgg atgccacctc cctgcacatt	180
gaatcgctga gcctgggaga tgagggaatc tacacctgcc aggagatcct gaatgtgact	240
cagtgggttc aagtgtggct gcagggtggc aatccccctc catcagctcc ccagtgtgg	300
gcacagatgg catcaggatc gttcatgttg cagcttacct gtcgctggga tgggggatac	360
cctgaccctg acttcctgtg gatagaagag ccaggaggtg taatcgtggg gaagtcaaag	420
ctgggggtgg aaatgctgag cgagtcccag ctgtcggatg gcaagaagtt caagtgtgtt	480
acaagccaca tagttgggccc agagtcgggc gccagctgca tgggtgcagat caggggtccc	540
tcccttctct ctgagcccat gaagacttgc ttcactgggg gcaatgtgac gcttacatgc	600
caggtgtctg gggcctaccc cctgccaag atcctgtggc tgaggaacct taccagccc	660
gaggtgatca tccagcctag cagccgccat ctcattaccc aggatggcca gaactccacc	720
ctcactatcc acaactgctc ccaggacctg gatgagggct actacatctg ccgagctgac	780
agccctgtag gggtagggga gatggaaatc tggctgagtg tgaaagaacc tttaaataac	840
gggggg	846

<210> SEQ ID NO 37

<211> LENGTH: 612

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 37

gagttggagc cacaatataga tggtcagacc tgggctgagc gggcacttcg ggagaatgaa	60
cgccacgcct tcacctgccg ggtggcaggg gggcctggca cccccagatt ggctgggtat	120
ctggatggac agctgcagga ggccagcacc tcaagactgc tgagcgtggg aggggagggc	180
ttctctggag gcaccagcac cttcactgtc actgccatc gggcccagca tgagctcaac	240

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Asp Gly Gln Thr Trp Ala Glu Arg Ala Leu Arg Glu Asn Glu Arg His
 35 40 45
 Ala Phe Thr Cys Arg Val Ala Gly Gly Pro Gly Thr Pro Arg Leu Ala
 50 55 60
 Trp Tyr Leu Asp Gly Gln Leu Gln Glu Ala Ser Thr Ser Arg Leu Leu
 65 70 75 80
 Ser Val Gly Gly Glu Ala Phe Ser Gly Gly Thr Ser Thr Phe Thr Val
 85 90 95
 Thr Ala His Arg Ala Gln His Glu Leu Asn Cys Ser Leu Gln Asp Pro
 100 105 110
 Arg Ser Gly Arg Ser Ala Asn Ala Ser Val Ile Leu Asn Val Gln Phe
 115 120 125
 Lys Pro Glu Ile Ala Gln Val Gly Ala Lys Tyr Gln Glu Ala Gln Gly
 130 135 140
 Pro Gly Leu Leu Val Val Leu Phe Ala Leu Val Arg Ala Asn Pro Pro
 145 150 155 160
 Ala Asn Val Thr Trp Ile Asp Gln Asp Gly Pro Val Thr Val Asn Thr
 165 170 175
 Ser Asp Phe Leu Val Leu Asp Ala Gln Asn Tyr Pro Trp Leu Thr Asn
 180 185 190
 His Thr Val Gln Leu Gln Leu Arg Ser Leu Ala His Asn Leu Ser Val
 195 200 205
 Val Ala Thr Asn Asp Val Gly Val Thr Ser Ala Ser Leu Pro Ala Pro
 210 215 220
 Gly Leu Leu Ala Thr Arg Val Glu
 225 230

<210> SEQ ID NO 40
 <211> LENGTH: 510
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 40

atccaggtga ccggtgtccaa ccctaccac gtggtgatcc tcttcagacc tgtgacctg	60
ccctgtacct accagatgac ctgcaccccc acgcaaccca tcgtcatctg gaagtacaag	120
tctttctgcc gggaccgcat cgccgatgcc ttctccccgg ccagcgtcga caaccagctc	180
aatgcccagc tggcagccgg gaaccaggc tacaaccct acgtcgagtg ccaggacagc	240
gtgcgcaccg tcagggtcgt ggccaccaag cagggaacg ctgtgacctt gggagattac	300
taccagggcc ggaggattac catcaccgga aatgctgacc tgacctttga ccagacggcg	360
tggggggaca gtggtgtgta ttactgctcc gtggtctcag ccaggacct ccagggaac	420
aatgaggcct acgcagagct catcgctctt gggaggacct cagggtggc tgagctetta	480
cctggttttc aggcggggcc catagaagac	510

<210> SEQ ID NO 41
 <211> LENGTH: 453
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 41

atccaggtga ccggtgtccaa ccctaccac gtggtgatcc tcttcagacc tgtgacctg	60
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cctgtacct accagatgac ctcgaccccc acgcaaccca tcgtcatctg gaagtacaag	120
tctttctgcc gggaccgcat cgcgatgcc ttctccccgg ccagcgtcga caaccagctc	180
aatgcccagc tggcagcggg gaaccaggc tacaaccctt acgtcgagtg ccaggacagc	240
gtgcgcacgg tcagggtcgt gggcaccagg cagggcaacg ctgtgacctt gggagattac	300
taccagggcc ggaggattac catcacggga aatgctgacc tgacctttga ccagacggcg	360
tggggggaca gtggtgtgta ttactgctcc gtggtctcag ccaggacact ccagggaac	420
aatgaggcct acgcagagct catcgctcct gac	453

<210> SEQ ID NO 42

<211> LENGTH: 1599

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 42

atggcgctgt tggccggcgg gctctccaga gggctgggct cccacccggc cgccgcaggc	60
cgggacgcgg tcgtcttcgt gtggtctctg cttagcacct ggtgcacagc tcctgccagg	120
gccatccagg tgaccgtgtc caacccttac cagtggtgta tcctcttcca gcctgtgacc	180
ctgccctgta cctaccagat gacctcgacc cccacgcaac ccatcgctcat ctggaagtac	240
aagtctttct gccgggaccg catcgccgat gccttctccc cggccagcgt cgacaaccag	300
ctcaatgccc agctggcagc cggaaccca ggctacaacc cctacgtcga gtgccaggac	360
agcgtgcgca ccgtcagggt cgtggccacc aagcagggca acgctgtgac cctgggagat	420
tactaccagg gccggaggat taccatcacc ggaaatgctg acctgacctt tgaccagacg	480
gcgtgggggg acagtgtgtg gtattactgc tccgtggtct cagcccagga cctccagggg	540
aacaatgagg cctacgcaga gctcatcgtc cttgtgtatg ccgccggcaa agcagccacc	600
tcagtggttc ccagcattta tgccccagc acctatgccc acctgtctcc cgccaagacc	660
ccacccccac cagctatgat tccatgggc cctgcctaca acgggtaccc tggaggatac	720
cctggagacg ttgacaggag tagctcagct ggtggccaag gctcctatgt acccctgctt	780
cgggacacgg acagcagtggt ggctctgaa gtccgcagtg gctacaggat tcaggccagc	840
cagcaggacg actccatgcg ggtcctgtac tacatggaga aggagctggc caacttcgac	900
ccttctcgac ctggcccccc cagtggccgt gtggagcggg ccatgagtga agtcacctcc	960
ctccacgagg acgactggcg atctcggcct tcccggggcc ctgcccctac ccgatccgg	1020
gatgaggagt ggggtggcca ctccccccgg agtcccaggg gatgggacca ggagcccgcc	1080
agggagcagg caggcggggg ctggcgggcc aggcggcccc gggcccgtc cgtggacgcc	1140
ctggacgacc tcaccccgcc gagcaccgcc gagtcaggga gcaggctctc cagagtaat	1200
gggtgggagaa gccgggccta catgcccccg cggagccgca gccgggacga cctctatgac	1260
caagacgact cgagggaact cccacgctcc cgggaccccc actacgacga cttcaggctt	1320
cgggagcgcc ctcttgccga cccagggtcc caccaccacc gtaccggga ccctcgggac	1380
aacggctcca ggtccgggga cctccctat gatggcgccg tactggagga ggctgtgagg	1440
aagaaggggt cggaggagag gaggagaccc cacaaggagg aggaggaaga ggcctactac	1500
ccgcccgccg cgcctccgta ctcgagacg gactcgagg cgteccgaga gcgcaggctc	1560
aagaagaact tggccctgag tcgggaaagt ttagtcgtc	1599

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<210> SEQ ID NO 43
<211> LENGTH: 1596
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 43
atggcgctgt tggccggcgg gctctccaga gggctgggct cccacccggc cgccgcaggc    60
cgggacgcgg tcgtottcgt gtggcttctg cttagcacct ggtgcacagc tcctgccagg    120
gccatccagg tgaccgtgtc caaccctac cacgtggta tcctottcca gctgtgacc    180
ctgccctgta cctaccagat gacctcgacc cccacgcaac ccategtcac ctggaagtac    240
aagtctttct gccgggaccg catcgccgat gccttctccc cggccagcgt cgacaaccag    300
ctcaatgccc agctggcagc cggaaccca ggctacaacc cctacgtcga gtgccaggac    360
agcgtgcgca ccgtcagggt cgtggccacc aagcagggca acgctgtgac cctgggagat    420
tactaccagg gccggaggat taccatcacc ggaaatgctg acctgacctt tgaccagacg    480
gcgtgggggg acagtgtgtg gtattactgc tccgtggtct cagcccagga cctccagggg    540
aacaatgagg cctacgcaga gctcatcgtc cttgtgtatg ccgccggcaa agcagccacc    600
tcagggtgtc ccagcattta tgccccagc acctatgccc acctgtctcc cgccaagacc    660
ccacccccac cagctatgat tcccatgggc cctgcctaca acgggtaccc tggaggatac    720
cctggagacg ttgacaggag tagctcagct ggtggccaag gctcctatgt acccctgctt    780
cgggacacgg acagcagtgt ggctctgtc cgcagtggct acaggattca ggccagccag    840
caggacgact ccatgcgggt cctgtactac atggagaagg agctggccaa cttcgaccct    900
tctcgacctg gccccccag tggccgtgtg gagcgggcca tgagtgaagt cacctccctc    960
cacgaggacg actggcgatc tcggccttcc cggggccctg ccctcaccac gatccgggat    1020
gaggagtggg gtggccactc cccccggagt ccaggggat gggaccagga gcccgccagg    1080
gagcaggcag gcgggggctg gcggggccagg cggccccggg cccgctccgt ggaogccctg    1140
gacgacctca ccccgccgag caccgccgag tcagggaaga ggtctccac gagtaatggt    1200
gggagaagcc gggcctacat gcccccgcg agccgcagcc gggacgacct ctatgaccaa    1260
gacgactcga gggacttccc acgctcccgg gacccccact acgacgacct caggctctcg    1320
gagcgccctc ctgccgaccc cagggtccac caccaccgta cccgggaccc tcgggacaac    1380
ggctccaggt ccggggaccc cccctatgat gggcggtac tggaggaggc tgtgaggaa    1440
aaggggtcgg aggagaggag gagacccac aaggaggagg aggaagaggc ctactaccg    1500
cccgcccgcc ccccgactc ggagaccgac tcgcaggcgt cccgagagcg cagggtcaag    1560
aagaacttgg ccctgagtcg ggaaagtta gtcgtc    1596

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<210> SEQ ID NO 44
<211> LENGTH: 1473
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 44
atccaggatga ccgtgtccaa cccctaccac gtggtgatcc tcttcagcc tgtgacctg    60
ccctgtacct accagatgac ctgcaccccc acgcaaccca tcgtcatctg gaagtacaag    120
tctttctgcc gggaccgcat cgccgatgcc ttctccccgg ccagcgtcga caaccagctc    180

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aatgcccagc	tggcagccgg	gaaccacaggc	tacaaccctt	acgtcagtg	ccaggacagc	240
gtgcgcacgc	tcagggtcgt	ggccaccaag	cagggcaacg	ctgtgacct	gggagattac	300
taccagggcc	ggaggattac	catcacggga	aatgctgacc	tgacctttga	ccagacggcg	360
tggggggaca	gtggtgtgta	ttactgctcc	gtggtctcag	cccaggacct	ccaggggaac	420
aatgaggcct	acgcagagct	catcgctctt	gtgtatgccg	ccggcaaagc	agccacctca	480
ggtgttccca	gcatttatgc	ccccagcacc	tatgcccacc	tgtctccgc	caagacccca	540
ccccaccag	ctatgattcc	catgggcctt	gcctacaacg	ggtaccctgg	aggataacct	600
ggagacgttg	acaggagtag	ctcagctggt	ggccaaggct	cctatgtacc	cctgcttcgg	660
gacacggaca	gcagtgtggc	ctctgtccgc	agtggctaca	ggattcaggc	cagccagcag	720
gacgactcca	tgcgggtcct	gtactacatg	gagaaggagc	tggccaactt	cgaccttct	780
cgacctggcc	ccccagtggt	ccgtgtggag	cgggccatga	gtgaagtca	ctccctccac	840
gaggacgact	ggcgatctcg	gccttcccgc	ggcctgccc	tcaccccgat	ccgggatgag	900
gagtggggtg	gccactcccc	ccggagtccc	aggggatggg	accaggagcc	cgccagggag	960
caggcaggcg	ggggctggcg	ggccaggcgg	ccccggggcc	gctccgtgga	cgccctggac	1020
gacctcacc	cgccgagcac	cgccgagtca	gggagcagg	ctcccacgag	taatggtggg	1080
agaagccggg	cctacatgcc	cccgcggagc	cgacccggg	acgacctcta	tgaccaagac	1140
gactcgaggg	acttcccacg	ctcccgggac	ccccactacg	acgacttcag	gtctcgggag	1200
cgccctctcg	cgacccccag	gtcccaccac	caccgtaccc	gggacctctg	ggacaacggc	1260
tccagggtccg	gggacctccc	ctatgatggg	cggtactggt	aggaggctgt	gaggaagaag	1320
gggtcggagg	agaggaggag	accccaacaag	gaggaggagg	aagaggccta	ctaccgccc	1380
gcgcgcgcgc	cgtactcgga	gaccgactcg	caggcgctcc	gagagcgag	gctcaagaag	1440
aacttgcccc	tgagtcggga	aagtttagtc	gtc			1473

<210> SEQ ID NO 45

<211> LENGTH: 1479

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 45

atggcgctgt	tggccggcgg	gctctccaga	gggctgggct	cccacccggc	cgccgcaggc	60
cgggacgcgg	tcgtcttcgt	gtggcttctg	cttagcacct	ggtgcacagc	tcttgcagg	120
gccatccagg	tgacctgtgc	caacccttac	cacgtggtga	tcctcttcca	gcctgtgacc	180
ctgccctgta	cctaccagat	gacctcgacc	cccacgcaac	ccatcgtcac	ctggaagtac	240
aagtctttct	gccgggaccg	catcgccgat	gccttctccc	cggccagcgt	cgacaaccag	300
ctcaatgccc	agctggcagc	cgggaacca	ggctacaacc	cctacgtcga	gtgccaggac	360
agcgtgcgca	ccgtcagggt	cgtggccacc	aagcagggca	acgtgtgac	cctgggagat	420
tactaccagg	gccggaggat	taccatcacc	ggaatgtatg	ccgcggcaa	agcagccacc	480
tcagggtgtc	ccagcattta	tgccccacgc	acctatgccc	acctgtctcc	cgccaagacc	540
ccacccccac	cagctatgat	tcccatgggc	cctgcctaca	acgggtaccc	tggaggatac	600
cctggagacg	ttgacaggag	tagctcagct	ggtggccaag	gctcctatgt	acccctgctt	660
cgggacacgg	acagcagtg	ggcctctgaa	gtccgcagtg	gctacaggat	tcaggccagc	720
cagcaggacg	actccatgcg	ggtcctgtac	tacatggaga	aggagctggc	caacttcgac	780

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ccttctcgac ctggccccc cagtggccgt gtggagcggg ccatgagtga agtcacctcc	840
ctccacgagg acgactggcg atctcggcct tcccggggcc ctgcccctac cccgatccgg	900
gatgaggagt ggggtggcca ctccccccg agtcccaggg gatgggacca ggagcccgcc	960
agggagcagg caggcggggg ctggcggggc aggcggcccc gggcccgctc cgtggacgcc	1020
ctggacgacc tcaccccgc gagcacgcc gagtcaggga gcaggtctcc cacgagtaat	1080
ggtgggagaa gccgggccta catgcccccg cggagccgca gccgggacga cctctatgac	1140
caagacgact cgagggaact cccacgctcc cgggaccccc actacgacga cttcaggctc	1200
cgggagcgcc ctctgcgca cccaggtcc caccaccacc gtaccggga ccctcgggac	1260
aacggctcca ggtccggga cctcccctat gatgggcggc tactggagga ggctgtgagg	1320
aagaaggggt cggaggagag gaggagaccc cacaaggagg aggaggaaga ggccactac	1380
ccgcccgcg cgccccgta ctggagacc gactcgcagg cgtcccaga gcgcaggctc	1440
aagaagaact tggccctgag tcgggaaagt ttagtcgtc	1479

<210> SEQ ID NO 46

<211> LENGTH: 1656

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 46

atggcgctgt tggccggcgg gctctccaga gggtggggt ccccccggc cgccgcaggc	60
cgggacgcgg tcgtcttcgt gtggtcttg cttagcacct ggtgcacagc tcctgccagg	120
gccatccagg tgaccgtgtc caaccctac cacgtggtga tcctcttcca gcctgtgacc	180
ctgcctgta cctaccagat gacctcgacc cccacgcaac ccatcgctcat ctggaagtac	240
aagtctttct gccgggacg catcgccgat gccttctccc cggccagcgt cgacaaccag	300
ctcaatgccc agctggcagc cgggaaccca ggctacaacc cctacgtcga gtgccaggac	360
agcgtgcgca ccgtcagggt cgtggccacc aagcagggca acgctgtgac cctgggagat	420
tactaccagg gccggaggat taccatcacc ggaaatgctg acctgacctt tgaccagacg	480
gcgtgggggg acagtgggtg gtattactgc tccgtggtct cagcccagga cctccagggg	540
aacaatgagg cctacgcaga gctcatcgtc cttgggagga cctcaggggt ggctgagctc	600
ttacctgggt ttcaggcggg gcccatagaa gtgtatgccg ccggcaaagc agccacctca	660
ggtgttccca gcatttatgc cccagcacc tatgcccacc tgtctccgc caagacccca	720
ccccaccag ctatgattcc catgggcctt gcctacaacg ggtaccctgg aggataccct	780
ggagacgttg acaggagtag ctacagtggt ggccaaggct cctatgtacc cctgcttcgg	840
gacacggaca gcagtgtggc ctctgaagtc cgcagtggct acaggattca ggccagccag	900
caggacgact ccatgcgggt cctgtactac atggagaagg agctggccaa cttcgaccct	960
tctcgacctg gccccccag tgcccggtg gagcgggcca tgagtgaagt cacctccctc	1020
cacgaggacg actggcgatc tcggccttcc cggggccctg cctcaccctc gatccgggat	1080
gaggagtggg gtggccactc ccccgaggat cccaggggat gggaccagga gcccgccagg	1140
gagcaggcag gcgggggctg gcggggccagg cggccccggg cccgctccgt ggacgccctg	1200
gacgacctca ccccgccgag caccgcccag tcagggagca ggtctccac gagtaatggt	1260
gggagaagcc gggcctacat gcccccgcg agccgcagcc gggacgacct ctatgaccaa	1320

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gacgactcga gggacttccc acgctcccg gacccccact acgacgactt caggtctcgg 1380
gagcgccctc ctgccgaccc caggtccac caccaccgta cccgggaccc tcgggacaac 1440
ggctccagg t cgggggaact cccctatgat gggcggtac tggaggaggc tgtgaggaag 1500
aaggggtcgg aggagaggag gagacccac aaggaggagg aggaagaggc ctactaccg 1560
cccgccgcgc cccgtactc ggagaccgac tcgcaggcgt cccgagagcg caggtcaag 1620
aagaacttgg ccctgagtcg ggaaagtta gtcgtc 1656

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<210> SEQ ID NO 47
<211> LENGTH: 492
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide

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<400> SEQUENCE: 47

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Ile Gln Val Thr Val Ser Asn Pro Tyr His Val Val Ile Leu Phe Gln
1          5          10          15
Pro Val Thr Leu Pro Cys Thr Tyr Gln Met Thr Ser Thr Pro Thr Gln
20         25         30
Pro Ile Val Ile Trp Lys Tyr Lys Ser Phe Cys Arg Asp Arg Ile Ala
35         40         45
Asp Ala Phe Ser Pro Ala Ser Val Asp Asn Gln Leu Asn Ala Gln Leu
50         55         60
Ala Ala Gly Asn Pro Gly Tyr Asn Pro Tyr Val Glu Cys Gln Asp Ser
65         70         75         80
Val Arg Thr Val Arg Val Val Ala Thr Lys Gln Gly Asn Ala Val Thr
85         90         95
Leu Gly Asp Tyr Tyr Gln Gly Arg Arg Ile Thr Ile Thr Gly Asn Ala
100        105        110
Asp Leu Thr Phe Asp Gln Thr Ala Trp Gly Asp Ser Gly Val Tyr Tyr
115        120        125
Cys Ser Val Val Ser Ala Gln Asp Leu Gln Gly Asn Asn Glu Ala Tyr
130        135        140
Ala Glu Leu Ile Val Leu Val Tyr Ala Ala Gly Lys Ala Ala Thr Ser
145        150        155        160
Gly Val Pro Ser Ile Tyr Ala Pro Ser Thr Tyr Ala His Leu Ser Pro
165        170        175
Ala Lys Thr Pro Pro Pro Pro Ala Met Ile Pro Met Gly Pro Ala Tyr
180        185        190
Asn Gly Tyr Pro Gly Gly Tyr Pro Gly Asp Val Asp Arg Ser Ser Ser
195        200        205
Ala Gly Gly Gln Gly Ser Tyr Val Pro Leu Leu Arg Asp Thr Asp Ser
210        215        220
Ser Val Ala Ser Glu Val Arg Ser Gly Tyr Arg Ile Gln Ala Ser Gln
225        230        235        240
Gln Asp Asp Ser Met Arg Val Leu Tyr Tyr Met Glu Lys Glu Leu Ala
245        250        255
Asn Phe Asp Pro Ser Arg Pro Gly Pro Pro Ser Gly Arg Val Glu Arg
260        265        270
Ala Met Ser Glu Val Thr Ser Leu His Glu Asp Asp Trp Arg Ser Arg
275        280        285
Pro Ser Arg Gly Pro Ala Leu Thr Pro Ile Arg Asp Glu Glu Trp Gly
290        295        300

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Gly His Ser Pro Arg Ser Pro Arg Gly Trp Asp Gln Glu Pro Ala Arg
 305 310 315 320
 Glu Gln Ala Gly Gly Gly Trp Arg Ala Arg Arg Pro Arg Ala Arg Ser
 325 330 335
 Val Asp Ala Leu Asp Asp Leu Thr Pro Pro Ser Thr Ala Glu Ser Gly
 340 345 350
 Ser Arg Ser Pro Thr Ser Asn Gly Gly Arg Ser Arg Ala Tyr Met Pro
 355 360 365
 Pro Arg Ser Arg Ser Arg Asp Asp Leu Tyr Asp Gln Asp Asp Ser Arg
 370 375 380
 Asp Phe Pro Arg Ser Arg Asp Pro His Tyr Asp Asp Phe Arg Ser Arg
 385 390 395 400
 Glu Arg Pro Pro Ala Asp Pro Arg Ser His His His Arg Thr Arg Asp
 405 410 415
 Pro Arg Asp Asn Gly Ser Arg Ser Gly Asp Leu Pro Tyr Asp Gly Arg
 420 425 430
 Leu Leu Glu Glu Ala Val Arg Lys Lys Gly Ser Glu Glu Arg Arg Arg
 435 440 445
 Pro His Lys Glu Glu Glu Glu Glu Ala Tyr Tyr Pro Pro Ala Pro Pro
 450 455 460
 Pro Tyr Ser Glu Thr Asp Ser Gln Ala Ser Arg Glu Arg Arg Leu Lys
 465 470 475 480
 Lys Asn Leu Ala Leu Ser Arg Glu Ser Leu Val Val
 485 490

<210> SEQ ID NO 48

<211> LENGTH: 491

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 48

Ile Gln Val Thr Val Ser Asn Pro Tyr His Val Val Ile Leu Phe Gln
 1 5 10 15
 Pro Val Thr Leu Pro Cys Thr Tyr Gln Met Thr Ser Thr Pro Thr Gln
 20 25 30
 Pro Ile Val Ile Trp Lys Tyr Lys Ser Phe Cys Arg Asp Arg Ile Ala
 35 40 45
 Asp Ala Phe Ser Pro Ala Ser Val Asp Asn Gln Leu Asn Ala Gln Leu
 50 55 60
 Ala Ala Gly Asn Pro Gly Tyr Asn Pro Tyr Val Glu Cys Gln Asp Ser
 65 70 75 80
 Val Arg Thr Val Arg Val Val Ala Thr Lys Gln Gly Asn Ala Val Thr
 85 90 95
 Leu Gly Asp Tyr Tyr Gln Gly Arg Arg Ile Thr Ile Thr Gly Asn Ala
 100 105 110
 Asp Leu Thr Phe Asp Gln Thr Ala Trp Gly Asp Ser Gly Val Tyr Tyr
 115 120 125
 Cys Ser Val Val Ser Ala Gln Asp Leu Gln Gly Asn Asn Glu Ala Tyr
 130 135 140
 Ala Glu Leu Ile Val Leu Val Tyr Ala Ala Gly Lys Ala Ala Thr Ser
 145 150 155 160
 Gly Val Pro Ser Ile Tyr Ala Pro Ser Thr Tyr Ala His Leu Ser Pro
 165 170 175

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Ala Lys Thr Pro Pro Pro Pro Ala Met Ile Pro Met Gly Pro Ala Tyr
180 185 190

Asn Gly Tyr Pro Gly Gly Tyr Pro Gly Asp Val Asp Arg Ser Ser Ser
195 200 205

Ala Gly Gly Gln Gly Ser Tyr Val Pro Leu Leu Arg Asp Thr Asp Ser
210 215 220

Ser Val Ala Ser Val Arg Ser Gly Tyr Arg Ile Gln Ala Ser Gln Gln
225 230 235 240

Asp Asp Ser Met Arg Val Leu Tyr Tyr Met Glu Lys Glu Leu Ala Asn
245 250 255

Phe Asp Pro Ser Arg Pro Gly Pro Pro Ser Gly Arg Val Glu Arg Ala
260 265 270

Met Ser Glu Val Thr Ser Leu His Glu Asp Asp Trp Arg Ser Arg Pro
275 280 285

Ser Arg Gly Pro Ala Leu Thr Pro Ile Arg Asp Glu Glu Trp Gly Gly
290 295 300

His Ser Pro Arg Ser Pro Arg Gly Trp Asp Gln Glu Pro Ala Arg Glu
305 310 315 320

Gln Ala Gly Gly Gly Trp Arg Ala Arg Arg Pro Arg Ala Arg Ser Val
325 330 335

Asp Ala Leu Asp Asp Leu Thr Pro Pro Ser Thr Ala Glu Ser Gly Ser
340 345 350

Arg Ser Pro Thr Ser Asn Gly Gly Arg Ser Arg Ala Tyr Met Pro Pro
355 360 365

Arg Ser Arg Ser Arg Asp Asp Leu Tyr Asp Gln Asp Asp Ser Arg Asp
370 375 380

Phe Pro Arg Ser Arg Asp Pro His Tyr Asp Asp Phe Arg Ser Arg Glu
385 390 395 400

Arg Pro Pro Ala Asp Pro Arg Ser His His His Arg Thr Arg Asp Pro
405 410 415

Arg Asp Asn Gly Ser Arg Ser Gly Asp Leu Pro Tyr Asp Gly Arg Leu
420 425 430

Leu Glu Glu Ala Val Arg Lys Lys Gly Ser Glu Glu Arg Arg Arg Pro
435 440 445

His Lys Glu Glu Glu Glu Glu Ala Tyr Tyr Pro Pro Ala Pro Pro Pro
450 455 460

Tyr Ser Glu Thr Asp Ser Gln Ala Ser Arg Glu Arg Arg Leu Lys Lys
465 470 475 480

Asn Leu Ala Leu Ser Arg Glu Ser Leu Val Val
485 490

<210> SEQ ID NO 49
 <211> LENGTH: 452
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 49

Ile Gln Val Thr Val Ser Asn Pro Tyr His Val Val Ile Leu Phe Gln
1 5 10 15

Pro Val Thr Leu Pro Cys Thr Tyr Gln Met Thr Ser Thr Pro Thr Gln
20 25 30

Pro Ile Val Ile Trp Lys Tyr Lys Ser Phe Cys Arg Asp Arg Ile Ala
35 40 45

[illegible]

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<210> SEQ ID NO 50
<211> LENGTH: 511
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 50

Ile Gln Val Thr Val Ser Asn Pro Tyr His Val Val Ile Leu Phe Gln
1             5             10             15

Pro Val Thr Leu Pro Cys Thr Tyr Gln Met Thr Ser Thr Pro Thr Gln
20             25             30

Pro Ile Val Ile Trp Lys Tyr Lys Ser Phe Cys Arg Asp Arg Ile Ala
35             40             45

Asp Ala Phe Ser Pro Ala Ser Val Asp Asn Gln Leu Asn Ala Gln Leu
50             55             60

Ala Ala Gly Asn Pro Gly Tyr Asn Pro Tyr Val Glu Cys Gln Asp Ser
65             70             75             80

Val Arg Thr Val Arg Val Val Ala Thr Lys Gln Gly Asn Ala Val Thr
85             90             95

Leu Gly Asp Tyr Tyr Gln Gly Arg Arg Ile Thr Ile Thr Gly Asn Ala
100            105            110

Asp Leu Thr Phe Asp Gln Thr Ala Trp Gly Asp Ser Gly Val Tyr Tyr
115            120            125

Cys Ser Val Val Ser Ala Gln Asp Leu Gln Gly Asn Asn Glu Ala Tyr
130            135            140

Ala Glu Leu Ile Val Leu Gly Arg Thr Ser Gly Val Ala Glu Leu Leu
145            150            155            160

Pro Gly Phe Gln Ala Gly Pro Ile Glu Val Tyr Ala Ala Gly Lys Ala
165            170            175

Ala Thr Ser Gly Val Pro Ser Ile Tyr Ala Pro Ser Thr Tyr Ala His
180            185            190

Leu Ser Pro Ala Lys Thr Pro Pro Pro Pro Ala Met Ile Pro Met Gly
195            200            205

Pro Ala Tyr Asn Gly Tyr Pro Gly Gly Tyr Pro Gly Asp Val Asp Arg
210            215            220

Ser Ser Ser Ala Gly Gly Gln Gly Ser Tyr Val Pro Leu Leu Arg Asp
225            230            235            240

Thr Asp Ser Ser Val Ala Ser Glu Val Arg Ser Gly Tyr Arg Ile Gln
245            250            255

Ala Ser Gln Gln Asp Asp Ser Met Arg Val Leu Tyr Tyr Met Glu Lys
260            265            270

Glu Leu Ala Asn Phe Asp Pro Ser Arg Pro Gly Pro Pro Ser Gly Arg
275            280            285

Val Glu Arg Ala Met Ser Glu Val Thr Ser Leu His Glu Asp Asp Trp
290            295            300

Arg Ser Arg Pro Ser Arg Gly Pro Ala Leu Thr Pro Ile Arg Asp Glu
305            310            315            320

Glu Trp Gly Gly His Ser Pro Arg Ser Pro Arg Gly Trp Asp Gln Glu
325            330            335

Pro Ala Arg Glu Gln Ala Gly Gly Gly Trp Arg Ala Arg Arg Pro Arg
340            345            350

Ala Arg Ser Val Asp Ala Leu Asp Asp Leu Thr Pro Pro Ser Thr Ala
355            360            365

Glu Ser Gly Ser Arg Ser Pro Thr Ser Asn Gly Gly Arg Ser Arg Ala

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370	375	380
Tyr Met Pro Pro Arg Ser Arg Ser Arg Asp Asp Leu Tyr Asp Gln Asp		
385	390	395 400
Asp Ser Arg Asp Phe Pro Arg Ser Arg Asp Pro His Tyr Asp Asp Phe		
	405	410 415
Arg Ser Arg Glu Arg Pro Pro Ala Asp Pro Arg Ser His His His Arg		
	420 425	430
Thr Arg Asp Pro Arg Asp Asn Gly Ser Arg Ser Gly Asp Leu Pro Tyr		
	435 440	445
Asp Gly Arg Leu Leu Glu Glu Ala Val Arg Lys Lys Gly Ser Glu Glu		
	450 455	460
Arg Arg Arg Pro His Lys Glu Glu Glu Glu Glu Ala Tyr Tyr Pro Pro		
465	470 475	480
Ala Pro Pro Pro Tyr Ser Glu Thr Asp Ser Gln Ala Ser Arg Glu Arg		
	485 490	495
Arg Leu Lys Lys Asn Leu Ala Leu Ser Arg Glu Ser Leu Val Val		
	500 505	510

<210> SEQ ID NO 51
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 51

gagaacttgg caggctctcc

20

<210> SEQ ID NO 52
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 52

cacacttccc agcagatgtc

20

<210> SEQ ID NO 53
 <211> LENGTH: 34
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 53

ctagctagcc accatggcag tcttattcct cctc

34

<210> SEQ ID NO 54
 <211> LENGTH: 30
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 54

cgcggaattcg cctgggcttg tgggcaggtg

30

<210> SEQ ID NO 55
 <211> LENGTH: 1662
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence

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<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 55

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atggcagtct tattcctcct cctgttecta tgtggaactc cccaggctgc agacaacatg      60
caggccatct atgtggcctt gggggaggca gtagagctgc catgtccctc accacctact      120
ctacatgggg acgaacacct gtcatggttc tgcagccctg cagcaggctc ctccaccacc      180
ctggtagccc aagtccaagt gggcaggcca gcccagacc ctggaaaacc aggaagggaa      240
tccaggctca gactgctggg gaactattct ttgtggttgg agggatccaa agaggaagat      300
gccgggcggt actggtgcgc tgtgctaggt cagcaccaca actaccagaa ctggagggtg      360
tacgacgtct tgggtgctca aggatcccag ttatctgcaa gggctgcaga tggatcccc      420
tgcaatgtcc tcctgtgctc tgtgttcccc agcagacgca tggactctgt gacctggcag      480
gaagggaagg gtcccgtgag gggccgtgtt cagtccttct ggggcagtga ggctgcctg      540
ctcttggtgt gtcttgggga ggggctttct gagcccagga gccgaagacc aagaatcatc      600
cgctgcctca tgactcacia caaaggggtc agctttagcc tggcagcctc catcgatgct      660
tctcctgccc tctgtgcccc ttccacgggc tgggacatgc cttggattct gatgctgctg      720
ctcacaatgg gccagggagt tgtcatcctg gccctcagca tcgtgctctg gaggcagagg      780
gtccgtgggg ctccaggcag agatgcctcg attcctcagt tcaaacccga aatccaggtc      840
tatgagaaca tccatttggc ccgtcttggc ccacctgccc acaagcccag gcgaattctg      900
cagtcgacgg taccgcgggc ccgggatcca ccggtcgcca ccatggtgag caagggcgag      960
gagctgttca ccgggggtgt gcccatcctg gtcgagctgg acggcgacgt aaacggccac     1020
aagttcagcg tgtccggcga gggcgagggc gatgccacct acggcaagct gacctgaag      1080
ttcatctgca ccaccggcaa gctgcccgtg ccttgggcca ccctcgtgac cacctgacc      1140
tacggcgtgc agtgcctcag ccgctacccc gaccacatga agcagcacga cttcttcaag      1200
tccgccatgc ccgaaggcta cgtccaggag cgcaccatct tcttcaagga cgacggcaac      1260
tacaagaccc ggcgcgaggt gaagtctgag ggcgacaccc tggatgaaccg catcgagctg      1320
aagggcatcg acttcaagga ggacggcaac atcctggggc acaagctgga gtacaactac      1380
aacagccaca acgtctatat catggccgac aagcagaaga acggcatcaa ggtgaacttc      1440
aagatccgcc acaacatcga ggacggcagc gtgcagctcg ccgaccacta ccagcagaac      1500
acccccatcg gcgacggccc cgtgctgctg cccgacaacc actacctgag caccagtc      1560
gccctgagca aagaccccaa cgagaagcgc gatcacatgg tctgctgga gttcgtgacc      1620
gccgcccggga tcactctcgg catggacgag ctgtacaagt aa                        1662

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<210> SEQ ID NO 56

<211> LENGTH: 553

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 56

```

Met Ala Val Leu Phe Leu Leu Leu Phe Leu Cys Gly Thr Pro Gln Ala
1           5           10          15

Ala Asp Asn Met Gln Ala Ile Tyr Val Ala Leu Gly Glu Ala Val Glu
20          25          30

Leu Pro Cys Pro Ser Pro Pro Thr Leu His Gly Asp Glu His Leu Ser
35          40          45

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Trp	Phe	Cys	Ser	Pro	Ala	Ala	Gly	Ser	Phe	Thr	Thr	Leu	Val	Ala	Gln
50					55					60					
Val	Gln	Val	Gly	Arg	Pro	Ala	Pro	Asp	Pro	Gly	Lys	Pro	Gly	Arg	Glu
65					70					75					80
Ser	Arg	Leu	Arg	Leu	Leu	Gly	Asn	Tyr	Ser	Leu	Trp	Leu	Glu	Gly	Ser
				85					90					95	
Lys	Glu	Glu	Asp	Ala	Gly	Arg	Tyr	Trp	Cys	Ala	Val	Leu	Gly	Gln	His
			100					105					110		
His	Asn	Tyr	Gln	Asn	Trp	Arg	Val	Tyr	Asp	Val	Leu	Val	Leu	Lys	Gly
		115					120					125			
Ser	Gln	Leu	Ser	Ala	Arg	Ala	Ala	Asp	Gly	Ser	Pro	Cys	Asn	Val	Leu
	130					135					140				
Leu	Cys	Ser	Val	Val	Pro	Ser	Arg	Arg	Met	Asp	Ser	Val	Thr	Trp	Gln
145					150					155					160
Glu	Gly	Lys	Gly	Pro	Val	Lys	Gly	Arg	Val	Gln	Ser	Phe	Trp	Gly	Ser
				165					170					175	
Glu	Ala	Ala	Leu	Leu	Leu	Val	Cys	Pro	Gly	Glu	Gly	Leu	Ser	Glu	Pro
			180					185					190		
Arg	Ser	Arg	Arg	Pro	Arg	Ile	Ile	Arg	Cys	Leu	Met	Thr	His	Asn	Lys
		195					200					205			
Gly	Val	Ser	Phe	Ser	Leu	Ala	Ala	Ser	Ile	Asp	Ala	Ser	Pro	Ala	Leu
	210					215					220				
Cys	Ala	Pro	Ser	Thr	Gly	Trp	Asp	Met	Pro	Trp	Ile	Leu	Met	Leu	Leu
225					230					235					240
Leu	Thr	Met	Gly	Gln	Gly	Val	Val	Ile	Leu	Ala	Leu	Ser	Ile	Val	Leu
			245						250					255	
Trp	Arg	Gln	Arg	Val	Arg	Gly	Ala	Pro	Gly	Arg	Asp	Ala	Ser	Ile	Pro
			260					265					270		
Gln	Phe	Lys	Pro	Glu	Ile	Gln	Val	Tyr	Glu	Asn	Ile	His	Leu	Ala	Arg
		275					280					285			
Leu	Gly	Pro	Pro	Ala	His	Lys	Pro	Arg	Arg	Ile	Leu	Gln	Ser	Thr	Val
	290					295					300				
Pro	Arg	Ala	Arg	Asp	Pro	Pro	Val	Ala	Thr	Met	Val	Ser	Lys	Gly	Glu
305					310					315					320
Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	Val	Glu	Leu	Asp	Gly	Asp
			325					330						335	
Val	Asn	Gly	His	Lys	Phe	Ser	Val	Ser	Gly	Glu	Gly	Glu	Gly	Asp	Ala
			340					345					350		
Thr	Tyr	Gly	Lys	Leu	Thr	Leu	Lys	Phe	Ile	Cys	Thr	Thr	Gly	Lys	Leu
		355					360					365			
Pro	Val	Pro	Trp	Pro	Thr	Leu	Val	Thr	Thr	Leu	Thr	Tyr	Gly	Val	Gln
	370					375					380				
Cys	Phe	Ser	Arg	Tyr	Pro	Asp	His	Met	Lys	Gln	His	Asp	Phe	Phe	Lys
385					390					395					400
Ser	Ala	Met	Pro	Glu											

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Val Tyr Ile Met Ala Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe
465 470 475 480

Lys Ile Arg His Asn Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His
485 490 495

Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp
500 505 510

Asn His Tyr Leu Ser Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu
515 520 525

Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile
530 535 540

Thr Leu Gly Met Asp Glu Leu Tyr Lys
545 550

<210> SEQ ID NO 57
<211> LENGTH: 891
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 57

```
atggcagctct ttttctctct cctgttctcta tgtggaactc cccaggctgc agacaacatg      60
caggccatct atgtggcctt gggggaggca gtagagctgc catgtccctc accacctact      120
ctacatgggg acgaacacct gtcatgggtc tgcagccctg cagcaggctc cttcaccacc      180
ctggtagccc aagtccaagt gggcaggcca gcccagacc ctggaaaacc aggaagggaa      240
tccaggctca gactgctggg gaactattct ttgtggttgg agggatccaa agaggaagat      300
gccggggcgt actggtgcgc tgtgctaggt cagcaccaca actaccagaa ctggagggtg      360
tacgacgtct tgggtctcaa aggatcccag ttatctgcaa gggtgcaga tggatcccc      420
tgcaatgtcc tcctgtgtc tgtggtcccc agcagacgca tggactctgt gacctggcag      480
gaagggaagg gtccctgtgag gggccgtgtt cagtccttct ggggcagtga ggctgccctg      540
ctcttggtgt gtctgggga ggggctttct gagcccagga gccgaagacc aagaatcacc      600
cgctgcctca tgactcacia caaaggggtc agctttagcc tggcagcctc catcgatgct      660
tctctgtccc tctgtgcccc ttccacgggc tgggacatgc cttggattct gatgtgctg      720
ctcacaatgg gccaggagtg tgtcatctc gccctcagca tcgtgctctg gaggcagagg      780
gtccgtgggg ctccaggcag agatgcctcg attcctcagt tcaaaccga aatccaggtc      840
tatgagaaca tccatttggc ccgtcttggc ccacctgccc acaagcccag g      891
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<210> SEQ ID NO 58
<211> LENGTH: 297
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 58

Met Ala Val Leu Phe Leu Leu Leu Phe Leu Cys Gly Thr Pro Gln Ala
1 5 10 15

Ala Asp Asn Met Gln Ala Ile Tyr Val Ala Leu Gly Glu Ala Val Glu
20 25 30

Leu Pro Cys Pro Ser Pro Pro Thr Leu His Gly Asp Glu His Leu Ser
35 40 45

Trp Phe Cys Ser Pro Ala Ala Gly Ser Phe Thr Thr Leu Val Ala Gln
50 55 60

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Val Gln Val Gly Arg Pro Ala Pro Asp Pro Gly Lys Pro Gly Arg Glu
 65 70 75 80
 Ser Arg Leu Arg Leu Leu Gly Asn Tyr Ser Leu Trp Leu Glu Gly Ser
 85 90 95
 Lys Glu Glu Asp Ala Gly Arg Tyr Trp Cys Ala Val Leu Gly Gln His
 100 105 110
 His Asn Tyr Gln Asn Trp Arg Val Tyr Asp Val Leu Val Leu Lys Gly
 115 120 125
 Ser Gln Leu Ser Ala Arg Ala Ala Asp Gly Ser Pro Cys Asn Val Leu
 130 135 140
 Leu Cys Ser Val Val Pro Ser Arg Arg Met Asp Ser Val Thr Trp Gln
 145 150 155 160
 Glu Gly Lys Gly Pro Val Lys Gly Arg Val Gln Ser Phe Trp Gly Ser
 165 170 175
 Glu Ala Ala Leu Leu Leu Val Cys Pro Gly Glu Gly Leu Ser Glu Pro
 180 185 190
 Arg Ser Arg Arg Pro Arg Ile Ile Arg Cys Leu Met Thr His Asn Lys
 195 200 205
 Gly Val Ser Phe Ser Leu Ala Ala Ser Ile Asp Ala Ser Pro Ala Leu
 210 215 220
 Cys Ala Pro Ser Thr Gly Trp Asp Met Pro Trp Ile Leu Met Leu Leu
 225 230 235 240
 Leu Thr Met Gly Gln Gly Val Val Ile Leu Ala Leu Ser Ile Val Leu
 245 250 255
 Trp Arg Gln Arg Val Arg Gly Ala Pro Gly Arg Asp Ala Ser Ile Pro
 260 265 270
 Gln Phe Lys Pro Glu Ile Gln Val Tyr Glu Asn Ile His Leu Ala Arg
 275 280 285
 Leu Gly Pro Pro Ala His Lys Pro Arg
 290 295

<210> SEQ ID NO 59

<211> LENGTH: 234

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 59

Met Ala Val Leu Phe Leu Leu Leu Phe Leu Cys Gly Thr Pro Gln Ala
 1 5 10 15
 Ala Asp Asn Met Gln Ala Ile Tyr Val Ala Leu Gly Glu Ala Val Glu
 20 25 30
 Leu Pro Cys Pro Ser Pro Pro Thr Leu His Gly Asp Glu His Leu Ser
 35 40 45
 Trp Phe Cys Ser Pro Ala Ala Gly Ser Phe Thr Thr Leu Val Ala Gln
 50 55 60
 Val Gln Val Gly Arg Pro Ala Pro Asp Pro Gly Lys Pro Gly Arg Glu
 65 70 75 80
 Ser Arg Leu Arg Leu Leu Gly Asn Tyr Ser Leu Trp Leu Glu Gly Ser
 85 90 95
 Lys Glu Glu Asp Ala Gly Arg Tyr Trp Cys Ala Val Leu Gly Gln His
 100 105 110
 His Asn Tyr Gln Asn Trp Arg Val Tyr Asp Val Leu Val Leu Lys Gly
 115 120 125

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Ser Gln Leu Ser Ala Arg Ala Ala Asp Gly Ser Pro Cys Asn Val Leu
 130 135 140
 Leu Cys Ser Val Val Pro Ser Arg Arg Met Asp Ser Val Thr Trp Gln
 145 150 155 160
 Glu Gly Lys Gly Pro Val Arg Gly Arg Val Gln Ser Phe Trp Gly Ser
 165 170 175
 Glu Ala Ala Leu Leu Leu Val Cys Pro Gly Glu Gly Leu Ser Glu Pro
 180 185 190
 Arg Ser Arg Arg Pro Arg Ile Ile Arg Cys Leu Met Thr His Asn Lys
 195 200 205
 Gly Val Ser Phe Ser Leu Ala Ala Ser Ile Asp Ala Ser Pro Ala Leu
 210 215 220
 Cys Ala Pro Ser Thr Gly Trp Asp Met Pro
 225 230

<210> SEQ ID NO 60
 <211> LENGTH: 413
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 60

Met Ala Ala Gly Gly Ser Ala Pro Glu Pro Arg Val Leu Val Cys Leu
 1 5 10 15
 Gly Ala Leu Leu Ala Gly Trp Val Ala Val Gly Leu Glu Ala Val Val
 20 25 30
 Ile Gly Glu Val His Glu Asn Val Thr Leu His Cys Gly Asn Ile Ser
 35 40 45
 Gly Leu Arg Gly Gln Val Thr Trp Tyr Arg Asn Asn Ser Glu Pro Val
 50 55 60
 Phe Leu Leu Ser Ser Asn Ser Ser Leu Arg Pro Ala Glu Pro Arg Phe
 65 70 75 80
 Ser Leu Val Asp Ala Thr Ser Leu His Ile Glu Ser Leu Ser Leu Gly
 85 90 95
 Asp Glu Gly Ile Tyr Thr Cys Gln Glu Ile Leu Asn Val Thr Gln Trp
 100 105 110
 Phe Gln Val Trp Leu Gln Val Ala Ser Gly Pro Tyr Gln Ile Glu Val
 115 120 125
 His Ile Val Ala Thr Gly Thr Leu Pro Asn Gly Thr Leu Tyr Ala Ala
 130 135 140
 Arg Gly Ser Gln Val Asp Phe Ser Cys Asn Ser Ser Ser Arg Pro Pro
 145 150 155 160
 Pro Val Val Glu Trp Trp Phe Gln Ala Leu Asn Ser Ser Ser Glu Ser
 165 170 175
 Phe Gly His Asn Leu Thr Val Asn Phe Phe Ser Leu Leu Ile Ser
 180 185 190
 Pro Asn Leu Gln Gly Asn Tyr Thr Cys Leu Ala Leu Asn Gln Leu Ser
 195 200 205
 Lys Arg His Arg Lys Val Thr Thr Glu Leu Leu Val Tyr Tyr Pro Pro
 210 215 220
 Pro Ser Ala Pro Gln Cys Trp Ala Gln Met Ala Ser Gly Ser Phe Met
 225 230 235 240
 Leu Gln Leu Thr Cys Arg Trp Asp Gly Gly Tyr Pro Asp Pro Asp Phe
 245 250 255

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Leu Trp Ile Glu Glu Pro Gly Gly Val Ile Val Gly Lys Ser Lys Leu
 260 265 270
 Gly Val Glu Met Leu Ser Glu Ser Gln Leu Ser Asp Gly Lys Lys Phe
 275 280 285
 Lys Cys Val Thr Ser His Ile Val Gly Pro Glu Ser Gly Ala Ser Cys
 290 295 300
 Met Val Gln Ile Arg Gly Pro Ser Leu Leu Ser Glu Pro Met Lys Thr
 305 310 315 320
 Cys Phe Thr Gly Gly Asn Val Thr Leu Thr Cys Gln Val Ser Gly Ala
 325 330 335
 Tyr Pro Pro Ala Lys Ile Leu Trp Leu Arg Asn Leu Thr Gln Pro Glu
 340 345 350
 Val Ile Ile Gln Pro Ser Ser Arg His Leu Ile Thr Gln Asp Gly Gln
 355 360 365
 Asn Ser Thr Leu Thr Ile His Asn Cys Ser Gln Asp Leu Asp Glu Gly
 370 375 380
 Tyr Tyr Ile Cys Arg Ala Asp Ser Pro Val Gly Val Arg Glu Met Glu
 385 390 395 400
 Ile Trp Leu Ser Val Lys Glu Pro Leu Asn Ile Gly Gly
 405 410

<210> SEQ ID NO 61
 <211> LENGTH: 312
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 61

Met Ala Ala Gly Gly Ser Ala Pro Glu Pro Arg Val Leu Val Cys Leu
 1 5 10 15
 Gly Ala Leu Leu Ala Gly Trp Val Ala Val Gly Leu Glu Ala Val Val
 20 25 30
 Ile Gly Glu Val His Glu Asn Val Thr Leu His Cys Gly Asn Ile Ser
 35 40 45
 Gly Leu Arg Gly Gln Val Thr Trp Tyr Arg Asn Asn Ser Glu Pro Val
 50 55 60
 Phe Leu Leu Ser Ser Asn Ser Ser Leu Arg Pro Ala Glu Pro Arg Phe
 65 70 75 80
 Ser Leu Val Asp Ala Thr Ser Leu His Ile Glu Ser Leu Ser Leu Gly
 85 90 95
 Asp Glu Gly Ile Tyr Thr Cys Gln Glu Ile Leu Asn Val Thr Gln Trp
 100 105 110
 Phe Gln Val Trp Leu Gln Val Ala Asn Pro Pro Pro Ser Ala Pro Gln
 115 120 125
 Cys Trp Ala Gln Met Ala Ser Gly Ser Phe Met Leu Gln Leu Thr Cys
 130 135 140
 Arg Trp Asp Gly Gly Tyr Pro Asp Pro Asp Phe Leu Trp Ile Glu Glu
 145 150 155 160
 Pro Gly Gly Val Ile Val Gly Lys Ser Lys Leu Gly Val Glu Met Leu
 165 170 175
 Ser Glu Ser Gln Leu Ser Asp Gly Lys Lys Phe Lys Cys Val Thr Ser
 180 185 190
 His Ile Val Gly Pro Glu Ser Gly Ala Ser Cys Met Val Gln Ile Arg
 195 200 205

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Gly Pro Ser Leu Leu Ser Glu Pro Met Lys Thr Cys Phe Thr Gly Gly
 210 215 220
 Asn Val Thr Leu Thr Cys Gln Val Ser Gly Ala Tyr Pro Pro Ala Lys
 225 230 235 240
 Ile Leu Trp Leu Arg Asn Leu Thr Gln Pro Glu Val Ile Ile Gln Pro
 245 250 255
 Ser Ser Arg His Leu Ile Thr Gln Asp Gly Gln Asn Ser Thr Leu Thr
 260 265 270
 Ile His Asn Cys Ser Gln Asp Leu Asp Glu Gly Tyr Tyr Ile Cys Arg
 275 280 285
 Ala Asp Ser Pro Val Gly Val Arg Glu Met Glu Ile Trp Leu Ser Val
 290 295 300
 Lys Glu Pro Leu Asn Ile Gly Gly
 305 310

<210> SEQ ID NO 62
 <211> LENGTH: 649
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 62

Met Gln Gln Asp Gly Leu Gly Val Gly Thr Arg Asn Gly Ser Gly Lys
 1 5 10 15
 Gly Arg Ser Val His Pro Ser Trp Pro Trp Cys Ala Pro Arg Pro Leu
 20 25 30
 Arg Tyr Phe Gly Arg Asp Ala Arg Ala Arg Arg Ala Gln Thr Ala Ala
 35 40 45
 Met Ala Leu Leu Ala Gly Gly Leu Ser Arg Gly Leu Gly Ser His Pro
 50 55 60
 Ala Ala Ala Gly Arg Asp Ala Val Val Phe Val Trp Leu Leu Leu Ser
 65 70 75 80
 Thr Trp Cys Thr Ala Pro Ala Arg Ala Ile Gln Val Thr Val Ser Asn
 85 90 95
 Pro Tyr His Val Val Ile Leu Phe Gln Pro Val Thr Leu Pro Cys Thr
 100 105 110
 Tyr Gln Met Thr Ser Thr Pro Thr Gln Pro Ile Val Ile Trp Lys Tyr
 115 120 125
 Lys Ser Phe Cys Arg Asp Arg Ile Ala Asp Ala Phe Ser Pro Ala Ser
 130 135 140
 Val Asp Asn Gln Leu Asn Ala Gln Leu Ala Ala Gly Asn Pro Gly Tyr
 145 150 155 160
 Asn Pro Tyr Val Glu Cys Gln Asp Ser Val Arg Thr Val Arg Val Val
 165 170 175
 Ala Thr Lys Gln Gly Asn Ala Val Thr Leu Gly Asp Tyr Tyr Gln Gly
 180 185 190
 Arg Arg Ile Thr Ile Thr Gly Asn Ala Asp Leu Thr Phe Asp Gln Thr
 195 200 205
 Ala Trp Gly Asp Ser Gly Val Tyr Tyr Cys Ser Val Val Ser Ala Gln
 210 215 220
 Asp Leu Gln Gly Asn Asn Glu Ala Tyr Ala Glu Leu Ile Val Leu Gly
 225 230 235 240
 Arg Thr Ser Gly Val Ala Glu Leu Leu Pro Gly Phe Gln Ala Gly Pro
 245 250 255

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Ile Glu Asp Trp Leu Phe Val Val Val Val Cys Leu Ala Ala Phe Leu
 260 265 270
 Ile Phe Leu Leu Leu Gly Ile Cys Trp Cys Gln Cys Cys Pro His Thr
 275 280 285
 Cys Cys Cys Tyr Val Arg Cys Pro Cys Cys Pro Asp Lys Cys Cys Cys
 290 295 300
 Pro Glu Ala Leu Tyr Ala Ala Gly Lys Ala Ala Thr Ser Gly Val Pro
 305 310 315 320
 Ser Ile Tyr Ala Pro Ser Thr Tyr Ala His Leu Ser Pro Ala Lys Thr
 325 330 335
 Pro Pro Pro Pro Ala Met Ile Pro Met Gly Pro Ala Tyr Asn Gly Tyr
 340 345 350
 Pro Gly Gly Tyr Pro Gly Asp Val Asp Arg Ser Ser Ser Ala Gly Gly
 355 360 365
 Gln Gly Ser Tyr Val Pro Leu Leu Arg Asp Thr Asp Ser Ser Val Ala
 370 375 380
 Ser Glu Val Arg Ser Gly Tyr Arg Ile Gln Ala Ser Gln Gln Asp Asp
 385 390 395 400
 Ser Met Arg Val Leu Tyr Tyr Met Glu Lys Glu Leu Ala Asn Phe Asp
 405 410 415
 Pro Ser Arg Pro Gly Pro Pro Ser Gly Arg Val Glu Arg Ala Met Ser
 420 425 430
 Glu Val Thr Ser Leu His Glu Asp Asp Trp Arg Ser Arg Pro Ser Arg
 435 440 445
 Gly Pro Ala Leu Thr Pro Ile Arg Asp Glu Glu Trp Gly Gly His Ser
 450 455 460
 Pro Arg Ser Pro Arg Gly Trp Asp Gln Glu Pro Ala Arg Glu Gln Ala
 465 470 475 480
 Gly Gly Gly Trp Arg Ala Arg Arg Pro Arg Ala Arg Ser Val Asp Ala
 485 490 495
 Leu Asp Asp Leu Thr Pro Pro Ser Thr Ala Glu Ser Gly Ser Arg Ser
 500 505 510
 Pro Thr Ser Asn Gly Gly Arg Ser Arg Ala Tyr Met Pro Pro Arg Ser
 515 520 525
 Arg Ser Arg Asp Asp Leu Tyr Asp Gln Asp Asp Ser Arg Asp Phe Pro
 530 535 540
 Arg Ser Arg Asp Pro His Tyr Asp Asp Phe Arg Ser Arg Glu Arg Pro
 545 550 555 560
 Pro Ala Asp Pro Arg Ser His His His Arg Thr Arg Asp Pro Arg Asp
 565 570 575
 Asn Gly Ser Arg Ser Gly Asp Leu Pro Tyr Asp Gly Arg Leu Leu Glu
 580 585 590
 Glu Ala Val Arg Lys Lys Gly Ser Glu Glu Arg Arg Arg Pro His Lys
 595 600 605
 Glu Glu Glu Glu Glu Ala Tyr Tyr Pro Pro Ala Pro Pro Pro Tyr Ser
 610 615 620
 Glu Thr Asp Ser Gln Ala Ser Arg Glu Arg Arg Leu Lys Lys Asn Leu
 625 630 635 640
 Ala Leu Ser Arg Glu Ser Leu Val Val
 645

<210> SEQ ID NO 63

<211> LENGTH: 630

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<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 63

Met  Gln  Gln  Asp  Gly  Leu  Gly  Val  Gly  Thr  Arg  Asn  Gly  Ser  Gly  Lys
 1          5          10          15

Gly  Arg  Ser  Val  His  Pro  Ser  Trp  Pro  Trp  Cys  Ala  Pro  Arg  Pro  Leu
          20          25          30

Arg  Tyr  Phe  Gly  Arg  Asp  Ala  Arg  Ala  Arg  Arg  Ala  Gln  Thr  Ala  Ala
          35          40          45

Met  Ala  Leu  Leu  Ala  Gly  Gly  Leu  Ser  Arg  Gly  Leu  Gly  Ser  His  Pro
 50          55          60

Ala  Ala  Ala  Gly  Arg  Asp  Ala  Val  Val  Phe  Val  Trp  Leu  Leu  Leu  Ser
 65          70          75          80

Thr  Trp  Cys  Thr  Ala  Pro  Ala  Arg  Ala  Ile  Gln  Val  Thr  Val  Ser  Asn
          85          90          95

Pro  Tyr  His  Val  Val  Ile  Leu  Phe  Gln  Pro  Val  Thr  Leu  Pro  Cys  Thr
          100          105          110

Tyr  Gln  Met  Thr  Ser  Thr  Pro  Thr  Gln  Pro  Ile  Val  Ile  Trp  Lys  Tyr
          115          120          125

Lys  Ser  Phe  Cys  Arg  Asp  Arg  Ile  Ala  Asp  Ala  Phe  Ser  Pro  Ala  Ser
          130          135          140

Val  Asp  Asn  Gln  Leu  Asn  Ala  Gln  Leu  Ala  Ala  Gly  Asn  Pro  Gly  Tyr
          145          150          155          160

Asn  Pro  Tyr  Val  Glu  Cys  Gln  Asp  Ser  Val  Arg  Thr  Val  Arg  Val  Val
          165          170          175

Ala  Thr  Lys  Gln  Gly  Asn  Ala  Val  Thr  Leu  Gly  Asp  Tyr  Tyr  Gln  Gly
          180          185          190

Arg  Arg  Ile  Thr  Ile  Thr  Gly  Asn  Ala  Asp  Leu  Thr  Phe  Asp  Gln  Thr
          195          200          205

Ala  Trp  Gly  Asp  Ser  Gly  Val  Tyr  Tyr  Cys  Ser  Val  Val  Ser  Ala  Gln
          210          215          220

Asp  Leu  Gln  Gly  Asn  Asn  Glu  Ala  Tyr  Ala  Glu  Leu  Ile  Val  Leu  Asp
          225          230          235          240

Trp  Leu  Phe  Val  Val  Val  Val  Cys  Leu  Ala  Ala  Phe  Leu  Ile  Phe  Leu
          245          250          255

Leu  Leu  Gly  Ile  Cys  Trp  Cys  Gln  Cys  Cys  Pro  His  Thr  Cys  Cys  Cys
          260          265          270

Tyr  Val  Arg  Cys  Pro  Cys  Cys  Pro  Asp  Lys  Cys  Cys  Cys  Pro  Glu  Ala
          275          280          285

Leu  Tyr  Ala  Ala  Gly  Lys  Ala  Ala  Thr  Ser  Gly  Val  Pro  Ser  Ile  Tyr
          290          295          300

Ala  Pro  Ser  Thr  Tyr  Ala  His  Leu  Ser  Pro  Ala  Lys  Thr  Pro  Pro  Pro
          305          310          315          320

Pro  Ala  Met  Ile  Pro  Met  Gly  Pro  Ala  Tyr  Asn  Gly  Tyr  Pro  Gly  Gly
          325          330          335

Tyr  Pro  Gly  Asp  Val  Asp  Arg  Ser  Ser  Ser  Ala  Gly  Gly  Gln  Gly  Ser
          340          345          350

Tyr  Val  Pro  Leu  Leu  Arg  Asp  Thr  Asp  Ser  Ser  Val  Ala  Ser  Glu  Val
          355          360          365

Arg  Ser  Gly  Tyr  Arg  Ile  Gln  Ala  Ser  Gln  Gln  Asp  Asp  Ser  Met  Arg
          370          375          380

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Val	Leu	Tyr	Tyr	Met	Glu	Lys	Glu	Leu	Ala	Asn	Phe	Asp	Pro	Ser	Arg	
385					390					395					400	
Pro	Gly	Pro	Pro	Ser	Gly	Arg	Val	Glu	Arg	Ala	Met	Ser	Glu	Val	Thr	
				405					410					415		
Ser	Leu	His	Glu	Asp	Asp	Trp	Arg	Ser	Arg	Pro	Ser	Arg	Gly	Pro	Ala	
			420					425					430			
Leu	Thr	Pro	Ile	Arg	Asp	Glu	Glu	Trp	Gly	Gly	His	Ser	Pro	Arg	Ser	
	435						440					445				
Pro	Arg	Gly	Trp	Asp	Gln	Glu	Pro	Ala	Arg	Glu	Gln	Ala	Gly	Gly	Gly	
	450					455					460					
Trp	Arg	Ala	Arg	Arg	Pro	Arg	Ala	Arg	Ser	Val	Asp	Ala	Leu	Asp	Asp	
465					470					475					480	
Leu	Thr	Pro	Pro	Ser	Thr	Ala	Glu	Ser	Gly	Ser	Arg	Ser	Pro	Thr	Ser	
				485					490					495		
Asn	Gly	Gly	Arg	Ser	Arg	Ala	Tyr	Met	Pro	Pro	Arg	Ser	Arg	Ser	Arg	
			500					505					510			
Asp	Asp	Leu	Tyr	Asp	Gln	Asp	Asp	Ser	Arg	Asp	Phe	Pro	Arg	Ser	Arg	
		515					520					525				
Asp	Pro	His	Tyr	Asp	Asp	Phe	Arg	Ser	Arg	Glu	Arg	Pro	Pro	Ala	Asp	
	530					535					540					
Pro	Arg	Ser	His	His	His	Arg	Thr	Arg	Asp	Pro	Arg	Asp	Asn	Gly	Ser	
545					550					555					560	
Arg	Ser	Gly	Asp	Leu	Pro	Tyr	Asp	Gly	Arg	Leu	Leu	Glu	Glu	Ala	Val	
				565				570						575		
Arg	Lys	Lys	Gly	Ser	Glu	Glu	Arg	Arg	Arg	Pro	His	Lys	Glu	Glu	Glu	
			580					585					590			
Glu	Glu	Ala	Tyr	Tyr	Pro	Pro	Ala	Pro	Pro	Pro	Tyr	Ser	Glu	Thr	Asp	
		595					600					605				
Ser	Gln	Ala	Ser	Arg	Glu	Arg	Arg	Leu	Lys	Lys	Asn	Leu	Ala	Leu	Ser	
	610					615					620					
Arg	Glu	Ser	Leu	Val	Val											
625					630											

<210> SEQ ID NO 64

<211> LENGTH: 588

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 64

Ala	Gln	Thr	Ala	Ala	Met	Ala	Leu	Leu	Ala	Gly	Gly	Leu	Ser	Arg	Gly	
1				5					10					15		
Leu	Gly	Ser	His	Pro	Ala	Ala	Ala	Gly	Arg	Asp	Ala	Val	Val	Phe	Val	
			20					25					30			
Trp	Leu	Leu	Leu	Ser	Thr	Trp	Cys	Thr	Ala	Pro	Ala	Arg	Ala	Ile	Gln	
	35						40					45				
Val	Thr	Val	Ser	Asn	Pro	Tyr	His	Val	Val	Ile	Leu	Phe	Gln	Pro	Val	
	50					55					60					
Thr	Leu	Pro	Cys	Thr	Tyr	Gln	Met	Thr	Ser	Thr	Pro	Thr	Gln	Pro	Ile	
65					70					75				80		
Val	Ile	Trp	Lys	Tyr	Lys	Ser	Phe	Cys	Arg	Asp	Arg	Ile	Ala	Asp	Ala	
			85					90						95		
Phe	Ser	Pro	Ala	Ser	Val	Asp	Asn	Gln	Leu	Asn	Ala	Gln	Leu	Ala	Ala	
			100					105						110		

Gly 115	Asn 120	Pro 125	Gly 130	Tyr 135	Asn 140	Pro 145	Tyr 150	Val 155	Glu 160	Cys 165	Gln 170	Asp 175	Ser 180	Val 185	Arg 190
Thr 130	Val 135	Arg 140	Val 145	Val 150	Ala 155	Thr 160	Lys 165	Gln 170	Gly 175	Asn 180	Ala 185	Val 190	Thr 195	Leu 200	Gly 205
Asp 145	Tyr 150	Tyr 155	Gln 160	Gly 165	Arg 170	Arg 175	Ile 180	Thr 185	Ile 190	Thr 195	Gly 200	Asn 205	Ala 210	Asp 215	Leu 220
Thr 160	Phe 165	Asp 170	Gln 175	Thr 180	Ala 185	Trp 190	Gly 195	Asp 200	Ser 205	Gly 210	Val 215	Tyr 220	Tyr 225	Cys 230	Ser 235
Val 175	Val 180	Ser 185	Ala 190	Gln 195	Asp 200	Leu 205	Gln 210	Asn 215	Asn 220	Glu 225	Ala 230	Tyr 235	Ala 240	Glu 245	
Leu 190	Ile 195	Val 200	Leu 205	Asp 210	Trp 215	Leu 220	Phe 225	Val 230	Val 235	Val 240	Val 245	Cys 250	Leu 255	Ala 260	Ala 265
Phe 205	Leu 210	Ile 215	Phe 220	Leu 225	Leu 230	Leu 235	Gly 240	Ile 245	Cys 250	Trp 255	Cys 260	Gln 265	Cys 270	Cys 275	Pro 280
His 220	Thr 225	Cys 230	Cys 235	Cys 240	Tyr 245	Val 250	Arg 255	Cys 260	Pro 265	Cys 270	Cys 275	Pro 280	Asp 285	Lys 290	Cys 295
Cys 235	Cys 240	Pro 245	Glu 250	Ala 255	Leu 260	Tyr 265	Ala 270	Ala 275	Gly 280	Lys 285	Ala 290	Ala 295	Thr 300	Ser 305	Gly 310
Val 250	Pro 255	Ser 260	Ile 265	Tyr 270	Ala 275	Pro 280	Ser 285	Thr 290	Tyr 295	Ala 300	His 305	Leu 310	Ser 315	Pro 320	Ala 325
Lys 265	Thr 270	Pro 275	Pro 280	Pro 285	Pro 290	Ala 295	Met 300	Ile 305	Pro 310	Met 315	Gly 320	Pro 325	Ala 330	Tyr 335	Asn 340
Gly 280	Tyr 285	Pro 290	Gly 295	Gly 300	Tyr 305	Pro 310	Gly 315	Asp 320	Val 325	Asp 330	Arg 335	Ser 340	Ser 345	Ser 350	Ala 355
Gly 300	Gly 305	Gln 310	Gly 315	Ser 320	Tyr 325	Val 330	Pro 335	Leu 340	Leu 345	Arg 350	Asp 355	Thr 360	Asp 365	Ser 370	Ser 375
Val 315	Ala 320	Ser 325	Glu 330	Val 335	Arg 340	Ser 345	Gly 350	Tyr 355	Arg 360	Ile 365	Gln 370	Ala 375	Ser 380	Gln 385	Gln 390
Asp 325	Asp 330	Ser 335	Met 340	Arg 345	Val 350	Leu 355	Tyr 360	Tyr 365	Met 370	Glu 375	Lys 380	Glu 385	Leu 390	Ala 395	Asn 400
Phe 340	Asp 345	Pro 350	Ser 355	Arg 360	Pro 365	Gly 370	Pro 375	Pro 380	Ser 385	Gly 390	Arg 395	Val 400	Glu 405	Arg 410	Ala 415
Met 355	Ser 360	Glu 365	Val 370	Thr 375	Ser 380	Leu 385	His 390	Glu 395	Asp 400	Asp 405	Trp 410	Arg 415	Ser 420	Arg 425	Pro 430
Ser 370	Arg 375	Gly 380	Pro 385	Ala 390	Leu 395	Thr 400	Pro 405	Ile 410	Arg 415	Asp 420	Glu 425	Glu 430	Trp 435	Gly 440	Gly 445
His 385	Ser 390	Pro 395	Arg 400	Ser 405	Pro 410	Arg 415	Gly 420	Trp 425	Asp 430	Gln 435	Glu 440	Pro 445	Ala 450	Arg 455	Glu 460
Gln 395	Ala 400	Gly 405	Gly 410	Gly 415	Trp 420	Arg 425	Ala 430	Arg 435	Pro 440	Arg 445	Ala 450	Arg 455	Ser 460	Val 465	
Asp 405	Ala 410	Leu 415	Asp 420	Asp 425	Leu 430	Thr 435	Pro 440	Pro 445	Ser 450	Thr 455	Ala 460	Glu 465	Ser 470	Gly 475	Ser 480
Arg 420	Ser 425	Pro 430	Thr 435	Ser 440	Asn 445	Gly 450	Gly 455	Arg 460	Arg 465	Ser 470	Arg 475	Ala 480	Tyr 485	Met 490	Pro 495
Pro 435	Arg 440	Ser 445	Arg 450	Ser 455	Arg 460	Asp 465	Asp 470	Leu 475	Tyr 480	Asp 485	Gln 490	Asp 495	Asp 500	Ser 505	Arg 510
Asp 450	Phe 455	Pro 460	Arg 465	Ser 470	Arg 475	Arg 480	Pro 485	His 490	Tyr 495	Asp 500	Asp 505	Phe 510	Arg 515	Ser 520	Arg 525
Glu 465	Arg 470	Pro 475	Pro 480	Ala 485	Asp 490										

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530	535	540
Pro His Lys Glu Glu Glu Glu Glu Ala Tyr Tyr Pro Pro Ala Pro Pro		
545	550	555 560
Pro Tyr Ser Glu Thr Asp Ser Gln Ala Ser Arg Glu Arg Arg Leu Lys		
	565	570 575
Lys Asn Leu Ala Leu Ser Arg Glu Ser Leu Val Val		
	580	585

<210> SEQ ID NO 65
 <211> LENGTH: 583
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 65

Met Ala Leu Leu Ala Gly Gly Leu Ser Arg Gly Leu Gly Ser His Pro	
1	5 10 15
Ala Ala Ala Gly Arg Asp Ala Val Val Phe Val Trp Leu Leu Leu Ser	
	20 25 30
Thr Trp Cys Thr Ala Pro Ala Arg Ala Ile Gln Val Thr Val Ser Asn	
	35 40 45
Pro Tyr His Val Val Ile Leu Phe Gln Pro Val Thr Leu Pro Cys Thr	
	50 55 60
Tyr Gln Met Thr Ser Thr Pro Thr Gln Pro Ile Val Ile Trp Lys Tyr	
65	70 75 80
Lys Ser Phe Cys Arg Asp Arg Ile Ala Asp Ala Phe Ser Pro Ala Ser	
	85 90 95
Val Asp Asn Gln Leu Asn Ala Gln Leu Ala Ala Gly Asn Pro Gly Tyr	
	100 105 110
Asn Pro Tyr Val Glu Cys Gln Asp Ser Val Arg Thr Val Arg Val Val	
	115 120 125
Ala Thr Lys Gln Gly Asn Ala Val Thr Leu Gly Asp Tyr Tyr Gln Gly	
	130 135 140
Arg Arg Ile Thr Ile Thr Gly Asn Ala Asp Leu Thr Phe Asp Gln Thr	
145	150 155 160
Ala Trp Gly Asp Ser Gly Val Tyr Tyr Cys Ser Val Val Ser Ala Gln	
	165 170 175
Asp Leu Gln Gly Asn Asn Glu Ala Tyr Ala Glu Leu Ile Val Leu Asp	
	180 185 190
Trp Leu Phe Val Val Val Val Cys Leu Ala Ala Phe Leu Ile Phe Leu	
	195 200 205
Leu Leu Gly Ile Cys Trp Cys Gln Cys Cys Pro His Thr Cys Cys Cys	
210	215 220
Tyr Val Arg Cys Pro Cys Cys Pro Asp Lys Cys Cys Cys Pro Glu Ala	
225	230 235 240
Leu Tyr Ala Ala Gly Lys Ala Ala Thr Ser Gly Val Pro Ser Ile Tyr	
	245 250 255
Ala Pro Ser Thr Tyr Ala His Leu Ser Pro Ala Lys Thr Pro Pro Pro	
	260 265 270
Pro Ala Met Ile Pro Met Gly Pro Ala Tyr Asn Gly Tyr Pro Gly Gly	
	275 280 285
Tyr Pro Gly Asp Val Asp Arg Asn Ser Ser Ala Gly Gly Gln Gly Ser	
290	295 300
Tyr Val Pro Leu Leu Arg Asp Thr Asp Ser Ser Val Ala Ser Glu Val	

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305	310	315	320
Arg Ser Gly Tyr Arg Ile Gln Ala Ser Gln Gln Asp Asp Ser Met Arg	325	330	335
Val Leu Tyr Tyr Met Glu Lys Glu Leu Ala Asn Phe Asp Pro Ser Arg	340	345	350
Pro Gly Pro Pro Ser Gly Arg Val Glu Arg Ala Met Ser Glu Val Thr	355	360	365
Ser Leu His Glu Asp Asp Trp Arg Ser Arg Pro Ser Arg Gly Pro Ala	370	375	380
Leu Thr Pro Ile Arg Asp Glu Glu Trp Gly Gly His Ser Pro Arg Ser	385	390	400
Pro Arg Gly Trp Asp Gln Glu Pro Ala Arg Glu Gln Ala Gly Gly Gly	405	410	415
Trp Arg Ala Arg Arg Pro Arg Ala Arg Ser Val Asp Ala Leu Asp Asp	420	425	430
Leu Thr Pro Pro Ser Thr Ala Glu Ser Gly Ser Arg Ser Pro Thr Ser	435	440	445
Asn Gly Gly Arg Arg Ser Arg Ala Tyr Met Pro Pro Arg Ser Arg Ser	450	455	460
Arg Asp Asp Leu Tyr Asp Gln Asp Asp Ser Arg Asp Phe Pro Arg Ser	465	470	475
Arg Asp Pro His Tyr Asp Asp Phe Arg Ser Arg Glu Arg Pro Pro Ala	485	490	495
Asp Pro Arg Ser His His His Arg Thr Arg Asp Pro Arg Asp Asn Gly	500	505	510
Ser Arg Ser Gly Asp Leu Pro Tyr Asp Gly Arg Leu Leu Glu Glu Ala	515	520	525
Val Arg Lys Lys Gly Ser Glu Glu Arg Arg Arg Pro His Lys Glu Glu	530	535	540
Glu Glu Glu Ala Tyr Tyr Pro Pro Ala Pro Pro Pro Tyr Ser Glu Thr	545	550	555
Asp Ser Gln Ala Ser Arg Glu Arg Arg Leu Lys Lys Asn Leu Ala Leu	565	570	575
Ser Arg Glu Ser Leu Val Val	580		

<210> SEQ ID NO 66

<211> LENGTH: 581

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 66

Met Gln Gln Asp Gly Leu Gly Val Gly Thr Arg Asn Gly Ser Gly Lys	1	5	10	15
Gly Arg Ser Val His Pro Ser Trp Pro Trp Cys Ala Pro Arg Pro Leu	20	25	30	
Arg Tyr Phe Gly Arg Asp Ala Arg Ala Arg Ala Gln Thr Ala Ala	35	40	45	
Met Ala Leu Leu Ala Gly Gly Leu Ser Arg Gly Leu Gly Ser His Pro	50	55	60	
Ala Ala Ala Gly Arg Asp Ala Val Val Phe Val Trp Leu Leu Leu Ser	65	70	75	80
Thr Trp Cys Thr Ala Pro Ala Arg Ala Ile Gln Val Thr Val Ser Asn				

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85								90				95			
Pro	Tyr	His	Val	Val	Ile	Leu	Phe	Gln	Pro	Val	Thr	Leu	Pro	Cys	Thr
			100					105					110		
Tyr	Gln	Met	Thr	Ser	Thr	Pro	Thr	Gln	Pro	Ile	Val	Ile	Trp	Lys	Tyr
		115					120					125			
Lys	Ser	Phe	Cys	Arg	Asp	Arg	Ile	Ala	Asp	Ala	Phe	Ser	Pro	Ala	Ser
	130					135					140				
Val	Asp	Asn	Gln	Leu	Asn	Ala	Gln	Leu	Ala	Ala	Gly	Asn	Pro	Gly	Tyr
145					150					155					160
Asn	Pro	Tyr	Val	Glu	Cys	Gln	Asp	Ser	Val	Arg	Thr	Val	Arg	Val	Val
			165						170					175	
Ala	Thr	Lys	Gln	Gly	Asn	Ala	Val	Thr	Leu	Gly	Asp	Tyr	Tyr	Gln	Gly
		180						185					190		
Arg	Arg	Ile	Thr	Ile	Thr	Gly	Asn	Ala	Asp	Leu	Thr	Phe	Asp	Gln	Thr
		195					200					205			
Ala	Trp	Gly	Asp	Ser	Gly	Val	Tyr	Tyr	Cys	Ser	Val	Val	Ser	Ala	Gln
	210					215					220				
Asp	Leu	Gln	Gly	Asn	Asn	Glu	Ala	Tyr	Ala	Glu	Leu	Ile	Val	Leu	Val
225					230					235					240
Tyr	Ala	Ala	Gly	Lys	Ala	Ala	Thr	Ser	Gly	Val	Pro	Ser	Ile	Tyr	Ala
			245						250					255	
Pro	Ser	Thr	Tyr	Ala	His	Leu	Ser	Pro	Ala	Lys	Thr	Pro	Pro	Pro	Pro
			260					265					270		
Ala	Met	Ile	Pro	Met	Gly	Pro	Ala	Tyr	Asn	Gly	Tyr	Pro	Gly	Gly	Tyr
	275						280					285			
Pro	Gly	Asp	Val	Asp	Arg	Ser	Ser	Ser	Ala	Gly	Gly	Gln	Gly	Ser	Tyr
	290					295					300				
Val	Pro	Leu	Leu	Arg	Asp	Thr	Asp	Ser	Ser	Val	Ala	Ser	Glu	Val	Arg
305					310					315					320
Ser	Gly	Tyr	Arg	Ile	Gln	Ala	Ser	Gln	Gln	Asp	Asp	Ser	Met	Arg	Val
			325					330						335	
Leu	Tyr	Tyr	Met	Glu	Lys	Glu	Leu	Ala	Asn	Phe	Asp	Pro	Ser	Arg	Pro
			340					345					350		
Gly	Pro	Pro	Ser	Gly	Arg	Val	Glu	Arg	Ala	Met	Ser	Glu	Val	Thr	Ser
		355				360						365			
Leu	His	Glu	Asp	Asp	Trp	Arg	Ser	Arg	Pro	Ser	Arg	Gly	Pro	Ala	Leu
	370					375					380				
Thr	Pro	Ile	Arg	Asp	Glu	Glu	Trp	Gly	Gly	His	Ser	Pro	Arg	Ser	Pro
385					390					395					400
Arg	Gly	Trp	Asp	Gln	Glu	Pro	Ala	Arg	Glu	Gln	Ala	Gly	Gly	Gly	Trp
			405						410					415	
Arg	Ala	Arg	Arg	Pro	Arg	Ala	Arg	Ser	Val	Asp	Ala	Leu	Asp	Asp	Leu
			420					425					430		
Thr	Pro	Pro	Ser	Thr	Ala	Glu	Ser	Gly	Ser	Arg	Ser	Pro	Thr	Ser	Asn
		435						440					445		
Gly	Gly	Arg	Ser	Arg	Ala	Tyr	Met	Pro	Pro	Arg	Ser	Arg	Ser	Arg	Asp
	450					455					460				
Asp	Leu	Tyr	Asp	Gln	Asp	Asp	Ser	Arg	Asp	Phe	Pro	Arg	Ser	Arg	Asp
465					470					475					480
Pro	His	Tyr	Asp	Asp	Phe	Arg	Ser	Arg	Glu	Arg	Pro	Pro	Ala	Asp	Pro
			485						490					495	
Arg	Ser	His	His	His	Arg	Thr	Arg	Asp	Pro	Arg	Asp	Asn	Gly	Ser	Arg
			500					505					510		

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Ser Gly Asp Leu Pro Tyr Asp Gly Arg Leu Leu Glu Glu Ala Val Arg
 515 520 525

Lys Lys Gly Ser Glu Glu Arg Arg Arg Pro His Lys Glu Glu Glu Glu
 530 535 540

Glu Ala Tyr Tyr Pro Pro Ala Pro Pro Pro Tyr Ser Glu Thr Asp Ser
 545 550 555 560

Gln Ala Ser Arg Glu Arg Arg Leu Lys Lys Asn Leu Ala Leu Ser Arg
 565 570 575

Glu Ser Leu Val Val
 580

<210> SEQ ID NO 67
 <211> LENGTH: 493
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 67

Met Ala Leu Leu Ala Gly Gly Leu Ser Arg Gly Leu Gly Ser His Pro
 1 5 10 15

Ala Ala Ala Gly Arg Asp Ala Val Val Phe Val Trp Leu Leu Leu Ser
 20 25 30

Thr Trp Cys Thr Ala Pro Ala Arg Ala Ile Gln Val Thr Val Ser Asn
 35 40 45

Pro Tyr His Val Val Ile Leu Phe Gln Pro Val Thr Leu Pro Cys Thr
 50 55 60

Tyr Gln Met Thr Ser Thr Pro Thr Gln Pro Ile Val Ile Trp Lys Tyr
 65 70 75 80

Lys Ser Phe Cys Arg Asp Arg Ile Ala Asp Ala Phe Ser Pro Ala Ser
 85 90 95

Val Asp Asn Gln Leu Asn Ala Gln Leu Ala Ala Gly Asn Pro Gly Tyr
 100 105 110

Asn Pro Tyr Val Glu Cys Gln Asp Ser Val Arg Thr Val Arg Val Val
 115 120 125

Ala Thr Lys Gln Gly Asn Ala Val Thr Leu Gly Asp Tyr Tyr Gln Gly
 130 135 140

Arg Arg Ile Thr Ile Thr Gly Met Tyr Ala Ala Gly Lys Ala Ala Thr
 145 150 155 160

Ser Gly Val Pro Ser Ile Tyr Ala Pro Ser Thr Tyr Ala His Leu Ser
 165 170 175

Pro Ala Lys Thr Pro Pro Pro Pro Ala Met Ile Pro Met Gly Pro Ala
 180 185 190

Tyr Asn Gly Tyr Pro Gly Gly Tyr Pro Gly Asp Val Asp Arg Ser Ser
 195 200 205

Ser Ala Gly Gly Gln Gly Ser Tyr Val Pro Leu Leu Arg Asp Thr Asp
 210 215 220

Ser Ser Val Ala Ser Glu Val Arg Ser Gly Tyr Arg Ile Gln Ala Ser
 225 230 235 240

Gln Gln Asp Asp Ser Met Arg Val Leu Tyr Tyr Met Glu Lys Glu Leu
 245 250 255

Ala Asn Phe Asp Pro Ser Arg Pro Gly Pro Pro Ser Gly Arg Val Glu
 260 265 270

Arg Ala Met Ser Glu Val Thr Ser Leu His Glu Asp Asp Trp Arg Ser
 275 280 285

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Arg Pro Ser Arg Gly Pro Ala Leu Thr Pro Ile Arg Asp Glu Glu Trp
 290 295 300
 Gly Gly His Ser Pro Arg Ser Pro Arg Gly Trp Asp Gln Glu Pro Ala
 305 310 315 320
 Arg Glu Gln Ala Gly Gly Gly Trp Arg Ala Arg Arg Pro Arg Ala Arg
 325 330 335
 Ser Val Asp Ala Leu Asp Asp Leu Thr Pro Pro Ser Thr Ala Glu Ser
 340 345 350
 Gly Ser Arg Ser Pro Thr Ser Asn Gly Gly Arg Ser Arg Ala Tyr Met
 355 360 365
 Pro Pro Arg Ser Arg Ser Arg Asp Asp Leu Tyr Asp Gln Asp Asp Ser
 370 375 380
 Arg Asp Phe Pro Arg Ser Arg Asp Pro His Tyr Asp Asp Phe Arg Ser
 385 390 395 400
 Arg Glu Arg Pro Pro Ala Asp Pro Arg Ser His His His Arg Thr Arg
 405 410 415
 Asp Pro Arg Asp Asn Gly Ser Arg Ser Gly Asp Leu Pro Tyr Asp Gly
 420 425 430
 Arg Leu Leu Glu Glu Ala Val Arg Lys Lys Gly Ser Glu Glu Arg Arg
 435 440 445
 Arg Pro His Lys Glu Glu Glu Glu Glu Ala Tyr Tyr Pro Pro Ala Pro
 450 455 460
 Pro Pro Tyr Ser Glu Thr Asp Ser Gln Ala Ser Arg Glu Arg Arg Leu
 465 470 475 480
 Lys Lys Asn Leu Ala Leu Ser Arg Glu Ser Leu Val Val
 485 490

<210> SEQ ID NO 68

<211> LENGTH: 602

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 68

Met Ala Leu Leu Ala Gly Gly Leu Ser Arg Gly Leu Gly Ser His Pro
 1 5 10 15
 Ala Ala Pro Gly Arg Asp Ala Val Val Phe Val Trp Leu Leu Ser
 20 25 30
 Thr Trp Cys Thr Ala Pro Ala Arg Ala Ile Gln Val Thr Val Ser Asn
 35 40 45
 Pro Tyr His Val Val Ile Leu Phe Gln Pro Val Thr Leu Pro Cys Thr
 50 55 60
 Tyr Gln Met Thr Ser Thr Pro Thr Gln Pro Ile Val Ile Trp Lys Tyr
 65 70 75 80
 Lys Ser Phe Cys Arg Asp Arg Ile Ala Asp Ala Phe Ser Pro Ala Ser
 85 90 95
 Val Asp Asn Gln Leu Asn Ala Gln Leu Ala Ala Gly Asn Pro Gly Tyr
 100 105 110
 Asn Pro Tyr Val Glu Cys Gln Asp Ser Val Arg Thr Val Arg Val Val
 115 120 125
 Ala Thr Lys Gln Gly Asn Ala Val Thr Leu Gly Asp Tyr Tyr Gln Gly
 130 135 140
 Arg Arg Ile Thr Ile Thr Gly Asn Ala Asp Leu Thr Phe Asp Gln Thr
 145 150 155 160

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Ala	Trp	Gly	Asp	Ser	Gly	Val	Tyr	Tyr	Cys	Ser	Val	Val	Ser	Ala	Gln	
				165					170					175		
Asp	Leu	Gln	Gly	Asn	Asn	Glu	Ala	Tyr	Ala	Glu	Leu	Ile	Val	Leu	Gly	
		180						185					190			
Arg	Thr	Ser	Gly	Val	Ala	Glu	Leu	Leu	Pro	Gly	Phe	Gln	Ala	Gly	Pro	
		195					200					205				
Met	Glu	Asp	Trp	Leu	Phe	Val	Val	Val	Val	Cys	Leu	Ala	Ala	Phe	Leu	
	210					215					220					
Ile	Phe	Leu	Leu	Leu	Gly	Ile	Cys	Trp	Cys	Gln	Cys	Cys	Pro	His	Thr	
225					230					235					240	
Cys	Cys	Cys	Tyr	Val	Arg	Cys	Pro	Cys	Cys	Pro	Asp	Lys	Cys	Cys	Cys	
			245					250					255			
Pro	Glu	Ala	Leu	Tyr	Ala	Ala	Gly	Lys	Ala	Ala	Thr	Ser	Gly	Val	Pro	
		260						265					270			
Ser	Ile	Tyr	Ala	Pro	Ser	Thr	Tyr	Ala	His	Leu	Ser	Pro	Ala	Lys	Thr	
	275					280						285				
Pro	Pro	Pro	Pro	Ala	Met	Ile	Pro	Met	Gly	Pro	Ala	Tyr	Asn	Gly	Tyr	
	290					295					300					
Pro	Gly	Gly	Tyr	Pro	Gly	Asp	Val	Asp	Arg	Ser	Ser	Ser	Ala	Gly	Gly	
305					310					315					320	
Gln	Gly	Ser	Tyr	Val	Pro	Leu	Leu	Arg	Asp	Thr	Asp	Ser	Ser	Val	Ala	
				325					330					335		
Ser	Glu	Val	Arg	Ser	Gly	Tyr	Arg	Ile	Gln	Ala	Ser	Gln	Gln	Asp	Asp	
		340						345					350			
Ser	Met	Arg	Val	Leu	Tyr	Tyr	Met	Glu	Lys	Glu	Leu	Ala	Asn	Phe	Asp	
	355					360						365				
Pro	Ser	Arg	Pro	Gly	Pro	Pro	Asn	Gly	Arg	Val	Glu	Arg	Ala	Met	Ser	
	370				375						380					
Glu	Val	Thr	Ser	Leu	His	Glu	Asp	Asp	Trp	Arg	Ser	Arg	Pro	Ser	Arg	
385					390					395					400	
Gly	Pro	Ala	Leu	Thr	Pro	Ile	Arg	Asp	Glu	Glu	Trp	Gly	Gly	His	Ser	
				405					410					415		
Pro	Arg	Ser	Pro	Arg	Gly	Trp	Asp	Gln	Glu	Pro	Pro	Arg	Glu	Gln	Ala	
			420					425					430			
Gly	Gly	Gly	Trp	Arg	Ala	Arg	Arg	Pro	Arg	Ala	Arg	Ser	Val	Asp	Ala	
	435					440						445				
Leu	Asp	Asp	Leu	Thr	Pro	Pro	Ser	Thr	Ala	Glu	Ser	Gly	Ser	Arg	Ser	
	450				455						460					
Pro	Thr	Ser	Ser	Gly	Gly	Arg	Arg	Gly	Arg	Ala	Tyr	Met	Pro	Pro	Arg	
465				470						475					480	
Ser	Arg	Ser	Arg	Asp	Asp	Leu	Tyr	Asp	Gln	Asp	Asp	Ser	Arg	Asp	Phe	
				485					490					495		
Pro	Arg	Ser	Arg	Asp	Ser	His	Tyr	Asp	Asp	Phe	Arg	Ser	Arg	Glu	Arg	
			500					505					510			
Pro	Pro	Ala	Asp	Pro	Arg	Ser	His	His	His	Arg	Thr	Arg	Asp	Pro	Arg	
		515					520					525				
Asp	His	Gly	Ser	Arg	Ser	Gly	Asp	Leu	Leu	Tyr	Asp	Gly	Arg	Leu	Leu	
	530					535					540					
Glu	Glu	Ala	Val	Arg	Lys	Lys	Gly	Ser	Glu	Glu	Arg	Arg	Arg	Pro	His	
545					550					555					560	
Lys	Glu	Glu	Glu	Glu	Glu	Ala	Tyr	Tyr	Pro	Pro	Ala	Pro	Pro	Pro	Tyr	
				565					570						575	

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Ser Glu Thr Asp Ser Gln Ala Ser Arg Glu Arg Arg Leu Lys Lys Asn
580 585 590

Leu Ala Leu Ser Arg Glu Ser Leu Val Val
595 600

<210> SEQ ID NO 69

<211> LENGTH: 534

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 69

Met Ala Leu Leu Ala Gly Gly Leu Ser Arg Gly Leu Gly Ser His Pro
1 5 10 15

Ala Ala Pro Gly Arg Asp Ala Val Val Phe Val Trp Leu Leu Leu Ser
20 25 30

Thr Trp Cys Thr Ala Pro Ala Arg Ala Ile Gln Val Thr Val Ser Asn
35 40 45

Pro Tyr His Val Val Ile Leu Phe Gln Pro Val Thr Leu Pro Cys Thr
50 55 60

Tyr Gln Met Thr Ser Thr Pro Thr Gln Pro Ile Val Ile Trp Lys Tyr
65 70 75 80

Lys Ser Phe Cys Arg Asp Arg Ile Ala Asp Ala Phe Ser Pro Ala Ser
85 90 95

Val Asp Asn Gln Leu Asn Ala Gln Leu Ala Ala Gly Asn Pro Gly Tyr
100 105 110

Asn Pro Tyr Val Glu Cys Gln Asp Ser Val Arg Thr Val Arg Val Val
115 120 125

Ala Thr Lys Gln Gly Asn Ala Val Thr Leu Gly Asp Tyr Tyr Gln Gly
130 135 140

Arg Arg Ile Thr Ile Thr Gly Asn Ala Asp Leu Thr Phe Asp Gln Thr
145 150 155 160

Ala Trp Gly Asp Ser Gly Val Tyr Tyr Cys Ser Val Val Ser Ala Gln
165 170 175

Asp Leu Gln Gly Asn Asn Glu Ala Tyr Ala Glu Leu Ile Val Leu Val
180 185 190

Tyr Ala Ala Gly Lys Ala Ala Thr Ser Gly Val Pro Ser Ile Tyr Ala
195 200 205

Pro Ser Thr Tyr Ala His Leu Ser Pro Ala Lys Thr Pro Pro Pro Pro
210 215 220

Ala Met Ile Pro Met Gly Pro Ala Tyr Asn Gly Tyr Pro Gly Gly Tyr
225 230 235 240

Pro Gly Asp Val Asp Arg Ser Ser Ser Ala Gly Gly Gln Gly Ser Tyr
245 250 255

Val Pro Leu Leu Arg Asp Thr Asp Ser Ser Val Ala Ser Glu Val Arg
260 265 270

Ser Gly Tyr Arg Ile Gln Ala Ser Gln Gln Asp Asp Ser Met Arg Val
275 280 285

Leu Tyr Tyr Met Glu Lys Glu Leu Ala Asn Phe Asp Pro Ser Arg Pro
290 295 300

Gly Pro Pro Asn Gly Arg Val Glu Arg Ala Met Ser Glu Val Thr Ser
305 310 315 320

Leu His Glu Asp Asp Trp Arg Ser Arg Pro Ser Arg Gly Pro Ala Leu
325 330 335

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Thr Pro Ile Arg Asp Glu Glu Trp Gly Gly His Ser Pro Arg Ser Pro
 340 345 350
 Arg Gly Trp Asp Gln Glu Pro Pro Arg Glu Gln Ala Gly Gly Gly Trp
 355 360 365
 Arg Ala Arg Arg Pro Arg Ala Arg Ser Val Asp Ala Leu Asp Asp Leu
 370 375 380
 Thr Pro Pro Ser Thr Ala Glu Ser Gly Ser Arg Ser Pro Thr Ser Ser
 385 390 395 400
 Gly Gly Arg Arg Gly Arg Ala Tyr Met Pro Pro Arg Ser Arg Ser Arg
 405 410 415
 Asp Asp Leu Tyr Asp Gln Asp Asp Ser Arg Asp Phe Pro Arg Ser Arg
 420 425 430
 Asp Ser His Tyr Asp Asp Phe Arg Ser Arg Glu Arg Pro Pro Ala Asp
 435 440 445
 Pro Arg Ser His His His Arg Thr Arg Asp Pro Arg Asp His Gly Ser
 450 455 460
 Arg Ser Gly Asp Leu Leu Tyr Asp Gly Arg Leu Leu Glu Glu Ala Val
 465 470 475 480
 Arg Lys Lys Gly Ser Glu Glu Arg Arg Arg Pro His Lys Glu Glu Glu
 485 490 495
 Glu Glu Ala Tyr Tyr Pro Pro Ala Pro Pro Pro Tyr Ser Glu Thr Asp
 500 505 510
 Ser Gln Ala Ser Arg Glu Arg Arg Leu Lys Lys Asn Leu Ala Leu Ser
 515 520 525
 Arg Glu Ser Leu Val Val
 530

<210> SEQ ID NO 70
 <211> LENGTH: 232
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 70

Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
 1 5 10 15
 Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
 20 25 30
 Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
 35 40 45
 Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
 50 55 60
 Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
 65 70 75 80
 Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
 85 90 95
 Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
 100 105 110
 Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
 115 120 125
 Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
 130 135 140
 Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
 145 150 155 160

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Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
 165 170 175
 Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
 180 185 190
 Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
 195 200 205
 Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
 210 215 220
 Ser Leu Ser Leu Ser Pro Gly Lys
 225 230

<210> SEQ ID NO 71
 <211> LENGTH: 466
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 71

Met Ala Val Leu Phe Leu Leu Leu Phe Leu Cys Gly Thr Pro Gln Ala
 1 5 10 15
 Ala Asp Asn Met Gln Ala Ile Tyr Val Ala Leu Gly Glu Ala Val Glu
 20 25 30
 Leu Pro Cys Pro Ser Pro Pro Thr Leu His Gly Asp Glu His Leu Ser
 35 40 45
 Trp Phe Cys Ser Pro Ala Ala Gly Ser Phe Thr Thr Leu Val Ala Gln
 50 55 60
 Val Gln Val Gly Arg Pro Ala Pro Asp Pro Gly Lys Pro Gly Arg Glu
 65 70 75 80
 Ser Arg Leu Arg Leu Leu Gly Asn Tyr Ser Leu Trp Leu Glu Gly Ser
 85 90 95
 Lys Glu Glu Asp Ala Gly Arg Tyr Trp Cys Ala Val Leu Gly Gln His
 100 105 110
 His Asn Tyr Gln Asn Trp Arg Val Tyr Asp Val Leu Val Leu Lys Gly
 115 120 125
 Ser Gln Leu Ser Ala Arg Ala Ala Asp Gly Ser Pro Cys Asn Val Leu
 130 135 140
 Leu Cys Ser Val Val Pro Ser Arg Arg Met Asp Ser Val Thr Trp Gln
 145 150 155 160
 Glu Gly Lys Gly Pro Val Arg Gly Arg Val Gln Ser Phe Trp Gly Ser
 165 170 175
 Glu Ala Ala Leu Leu Leu Val Cys Pro Gly Glu Gly Leu Ser Glu Pro
 180 185 190
 Arg Ser Arg Arg Pro Arg Ile Ile Arg Cys Leu Met Thr His Asn Lys
 195 200 205
 Gly Val Ser Phe Ser Leu Ala Ala Ser Ile Asp Ala Ser Pro Ala Leu
 210 215 220
 Cys Ala Pro Ser Thr Gly Trp Asp Met Pro Glu Pro Lys Ser Ser Asp
 225 230 235 240
 Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
 245 250 255
 Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
 260 265 270
 Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
 275 280 285

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Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
 290          295          300

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
 305          310          315          320

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
          325          330          335

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
          340          345          350

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
          355          360          365

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
 370          375          380

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 385          390          395          400

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
          405          410          415

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
          420          425          430

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
          435          440          445

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
 450          455          460

Gly Lys
465

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<210> SEQ ID NO 72
<211> LENGTH: 645
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide

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<400> SEQUENCE: 72

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Met Ala Ala Gly Gly Ser Ala Pro Glu Pro Arg Val Leu Val Cys Leu
 1          5          10          15

Gly Ala Leu Leu Ala Gly Trp Val Ala Val Gly Leu Glu Ala Val Val
          20          25          30

Ile Gly Glu Val His Glu Asn Val Thr Leu His Cys Gly Asn Ile Ser
          35          40          45

Gly Leu Arg Gly Gln Val Thr Trp Tyr Arg Asn Asn Ser Glu Pro Val
          50          55          60

Phe Leu Leu Ser Ser Asn Ser Ser Leu Arg Pro Ala Glu Pro Arg Phe
 65          70          75          80

Ser Leu Val Asp Ala Thr Ser Leu His Ile Glu Ser Leu Ser Leu Gly
          85          90          95

Asp Glu Gly Ile Tyr Thr Cys Gln Glu Ile Leu Asn Val Thr Gln Trp
          100          105          110

Phe Gln Val Trp Leu Gln Val Ala Ser Gly Pro Tyr Gln Ile Glu Val
          115          120          125

His Ile Val Ala Thr Gly Thr Leu Pro Asn Gly Thr Leu Tyr Ala Ala
          130          135          140

Arg Gly Ser Gln Val Asp Phe Ser Cys Asn Ser Ser Ser Arg Pro Pro
 145          150          155          160

Pro Val Val Glu Trp Trp Phe Gln Ala Leu Asn Ser Ser Ser Glu Ser
          165          170          175

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Phe 180	Gly	His	Asn	Leu	Thr	Val	Asn	Phe 185	Phe	Ser	Leu	Leu	Leu 190	Ser	
Pro 195	Asn	Leu	Gln	Gly	Asn	Tyr	Thr 200	Cys	Leu	Ala	Leu	Asn 205	Gln	Leu	Ser
Lys 210	Arg	His	Arg	Lys	Val	Thr 215	Thr	Glu	Leu	Leu	Val 220	Tyr	Tyr	Pro	Pro
Pro 225	Ser	Ala	Pro	Gln	Cys 230	Trp	Ala	Gln	Met	Ala 235	Ser	Gly	Ser	Phe	Met 240
Leu	Gln	Leu	Thr	Cys 245	Arg	Trp	Asp	Gly	Gly 250	Tyr	Pro	Asp	Pro	Asp	Phe 255
Leu	Trp	Ile	Glu 260	Glu	Pro	Gly	Gly	Val 265	Ile	Val	Gly	Lys 270	Ser	Lys	Leu
Gly	Val	Glu 275	Met	Leu	Ser	Glu	Ser 280	Gln	Leu	Ser	Asp	Gly 285	Lys	Lys	Phe
Lys 290	Cys	Val	Thr	Ser	His	Ile 295	Val	Gly	Pro	Glu	Ser 300	Gly	Ala	Ser	Cys
Met 305	Val	Gln	Ile	Arg	Gly 310	Pro	Ser	Leu	Leu	Ser 315	Glu	Pro	Met	Lys	Thr 320
Cys	Phe	Thr	Gly 325	Gly	Asn	Val	Thr	Leu	Thr 330	Cys	Gln	Val	Ser	Gly 335	Ala
Tyr	Pro	Pro	Ala 340	Lys	Ile	Leu	Trp	Leu	Arg	Asn	Leu	Thr 350	Gln	Pro	Glu
Val	Ile	Ile 355	Gln	Pro	Ser	Ser	Arg 360	His	Leu	Ile	Thr	Gln 365	Asp	Gly	Gln
Asn 370	Ser	Thr	Leu	Thr	Ile	His 375	Asn	Cys	Ser	Gln	Asp 380	Leu	Asp	Glu	Gly
Tyr 385	Tyr	Ile	Cys	Arg	Ala 390	Asp	Ser	Pro	Val	Gly 395	Val	Arg	Glu	Met	Glu 400
Ile	Trp	Leu	Ser	Val 405	Lys	Glu	Pro	Leu	Asn 410	Ile	Gly	Gly	Glu	Pro 415	Lys
Ser	Ser	Asp	Lys 420	Thr	His	Thr	Cys	Pro 425	Pro	Cys	Pro	Ala	Pro 430	Glu	Leu
Leu	Gly	Gly 435	Pro	Ser	Val	Phe	Leu 440	Phe	Pro	Pro	Lys	Pro 445	Lys	Asp	Thr
Leu	Met	Ile	Ser	Arg	Thr 455	Pro	Glu	Val	Thr	Cys	Val 460	Val	Val	Asp	Val
Ser 465	His	Glu	Asp	Pro	Glu 470	Val	Lys	Phe	Asn	Trp 475	Tyr	Val	Asp	Gly	Val 480
Glu	Val	His	Asn	Ala 485	Lys	Thr	Lys	Pro	Arg	Glu 490	Glu	Gln	Tyr	Asn 495	Ser
Thr	Tyr	Arg	Val 500	Val	Ser	Val	Leu	Thr 505	Val	Leu	His	Gln	Asp	Trp	Leu
Asn	Gly	Lys 515	Glu	Tyr	Lys	Cys	Lys 520	Val	Ser	Asn	Lys	Ala 525	Leu	Pro	Ala
Pro	Ile	Glu	Lys	Thr	Ile	Ser 535	Lys	Ala	Lys	Gly	Gln 540	Pro	Arg	Glu	Pro
Gln 545	Val	Tyr	Thr	Leu	Pro 550	Pro	Ser	Arg	Asp	Glu 555	Leu	Thr	Lys	Asn	Gln 560
Val	Ser	Leu	Thr	Cys 565	Leu	Val	Lys	Gly	Phe	Tyr 570	Pro	Ser	Asp	Ile	Ala 575
Val	Glu	Trp	Glu 580	Ser	Asn	Gly	Gln	Pro 585	Glu	Asn	Asn	Tyr	Lys 590	Thr	Thr
Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu

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595	600	605
Thr Val Asp Lys Ser Arg	Trp Gln Gln Gly Asn	Val Phe Ser Cys Ser
610	615	620
Val Met His Glu Ala Leu	His Asn His Tyr Thr	Gln Lys Ser Leu Ser
625	630	635 640
Leu Ser Pro Gly Lys		
645		
<210> SEQ ID NO 73		
<211> LENGTH: 544		
<212> TYPE: PRT		
<213> ORGANISM: Artificial sequence		
<220> FEATURE:		
<223> OTHER INFORMATION: Synthetic polypeptide		
<400> SEQUENCE: 73		
Met Ala Ala Gly Gly Ser Ala Pro Glu Pro Arg Val Leu Val Cys Leu		
1	5	10 15
Gly Ala Leu Leu Ala Gly Trp Val Ala Val Gly Leu Glu Ala Val Val		
	20	25 30
Ile Gly Glu Val His Glu Asn Val Thr Leu His Cys Gly Asn Ile Ser		
	35	40 45
Gly Leu Arg Gly Gln Val Thr Trp Tyr Arg Asn Asn Ser Glu Pro Val		
	50	55 60
Phe Leu Leu Ser Ser Asn Ser Ser Leu Arg Pro Ala Glu Pro Arg Phe		
65	70	75 80
Ser Leu Val Asp Ala Thr Ser Leu His Ile Glu Ser Leu Ser Leu Gly		
	85	90 95
Asp Glu Gly Ile Tyr Thr Cys Gln Glu Ile Leu Asn Val Thr Gln Trp		
	100	105 110
Phe Gln Val Trp Leu Gln Val Ala Asn Pro Pro Pro Ser Ala Pro Gln		
	115	120 125
Cys Trp Ala Gln Met Ala Ser Gly Ser Phe Met Leu Gln Leu Thr Cys		
	130	135 140
Arg Trp Asp Gly Gly Tyr Pro Asp Pro Asp Phe Leu Trp Ile Glu Glu		
145	150	155 160
Pro Gly Gly Val Ile Val Gly Lys Ser Lys Leu Gly Val Glu Met Leu		
	165	170 175
Ser Glu Ser Gln Leu Ser Asp Gly Lys Lys Phe Lys Cys Val Thr Ser		
	180	185 190
His Ile Val Gly Pro Glu Ser Gly Ala Ser Cys Met Val Gln Ile Arg		
	195	200 205
Gly Pro Ser Leu Leu Ser Glu Pro Met Lys Thr Cys Phe Thr Gly Gly		
	210	215 220
Asn Val Thr Leu Thr Cys Gln Val Ser Gly Ala Tyr Pro Pro Ala Lys		
225	230	235 240
Ile Leu Trp Leu Arg Asn Leu Thr Gln Pro Glu Val Ile Ile Gln Pro		
	245	250 255
Ser Ser Arg His Leu Ile Thr Gln Asp Gly Gln Asn Ser Thr Leu Thr		
	260	265 270
Ile His Asn Cys Ser Gln Asp Leu Asp Glu Gly Tyr Tyr Ile Cys Arg		
	275	280 285
Ala Asp Ser Pro Val Gly Val Arg Glu Met Glu Ile Trp Leu Ser Val		
	290	295 300
Lys Glu Pro Leu Asn Ile Gly Gly Glu Pro Lys Ser Ser Asp Lys Thr		

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305	310	315	320
His Thr Cys Pro	Pro Cys Pro Ala Pro	Glu Leu Leu Gly Gly Pro Ser	
	325	330	335
Val Phe Leu Phe	Pro Pro Lys Pro	Lys Asp Thr Leu Met Ile Ser Arg	
	340	345	350
Thr Pro Glu Val	Thr Cys Val Val Val	Asp Val Ser His Glu Asp Pro	
	355	360	365
Glu Val Lys Phe	Asn Trp Tyr Val	Asp Gly Val Glu Val His Asn Ala	
	370	375	380
Lys Thr Lys Pro	Arg Glu Glu Gln Tyr	Asn Ser Thr Tyr Arg Val Val	
	385	390	395
Ser Val Leu Thr	Val Leu His Gln Asp	Trp Leu Asn Gly Lys Glu Tyr	
	405	410	415
Lys Cys Lys Val	Ser Asn Lys Ala Leu	Pro Ala Pro Ile Glu Lys Thr	
	420	425	430
Ile Ser Lys Ala	Lys Gly Gln Pro	Arg Glu Pro Gln Val Tyr Thr Leu	
	435	440	445
Pro Pro Ser Arg	Asp Glu Leu Thr	Lys Asn Gln Val Ser Leu Thr Cys	
	450	455	460
Leu Val Lys Gly	Phe Tyr Pro Ser	Asp Ile Ala Val Glu Trp Glu Ser	
	465	470	475
Asn Gly Gln Pro	Glu Asn Asn Tyr	Lys Thr Thr Pro Pro Val Leu Asp	
	485	490	495
Ser Asp Gly Ser	Phe Phe Leu Tyr	Ser Lys Leu Thr Val Asp Lys Ser	
	500	505	510
Arg Trp Gln Gln	Gly Asn Val Phe Ser	Cys Ser Val Met His Glu Ala	
	515	520	525
Leu His Asn His	Tyr Thr Gln Lys	Ser Leu Ser Leu Ser Pro Gly Lys	
	530	535	540

<210> SEQ ID NO 74

<211> LENGTH: 464

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 74

Met Ala Leu Pro	Pro Gly Pro Ala Ala	Leu Arg His Thr Leu Leu Leu
1	5	10
Leu Pro Ala Leu	Leu Ser Ser Gly Trp	Gly Glu Leu Glu Pro Gln Ile
20	25	30
Asp Gly Gln Thr	Trp Ala Glu Arg Ala	Leu Arg Glu Asn Glu Arg His
35	40	45
Ala Phe Thr Cys	Arg Val Ala Gly Gly	Pro Gly Thr Pro Arg Leu Ala
50	55	60
Trp Tyr Leu Asp	Gly Gln Leu Gln Glu	Ala Ser Thr Ser Arg Leu Leu
65	70	75
Ser Val Gly Gly	Glu Ala Phe Ser Gly	Gly Thr Ser Thr Phe Thr Val
85	90	95
Thr Ala His Arg	Ala Gln His Glu Leu	Asn Cys Ser Leu Gln Asp Pro
100	105	110
Arg Ser Gly Arg	Ser Ala Asn Ala Ser	Val Ile Leu Asn Val Gln Phe
115	120	125
Lys Pro Glu Ile	Ala Gln Val Gly Ala	Lys Tyr Gln Glu Ala Gln Gly

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130	135	140
Pro Gly Leu Leu Val Val Leu Phe Ala Leu Val Arg Ala Asn Pro Pro		
145	150	155 160
Ala Asn Val Thr Trp Ile Asp Gln Asp Gly Pro Val Thr Val Asn Thr		
	165	170 175
Ser Asp Phe Leu Val Leu Asp Ala Gln Asn Tyr Pro Trp Leu Thr Asn		
	180	185 190
His Thr Val Gln Leu Gln Leu Arg Ser Leu Ala His Asn Leu Ser Val		
	195	200 205
Val Ala Thr Asn Asp Val Gly Val Thr Ser Ala Ser Leu Pro Ala Pro		
	210	215 220
Gly Leu Leu Ala Thr Arg Val Glu Glu Pro Lys Ser Ser Asp Lys Thr		
	225	230 235 240
His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser		
	245	250 255
Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg		
	260	265 270
Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro		
	275	280 285
Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala		
	290	295 300
Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val		
	305	310 315 320
Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr		
	325	330 335
Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr		
	340	345 350
Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu		
	355	360 365
Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys		
	370	375 380
Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser		
	385	390 395 400
Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp		
	405	410 415
Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser		
	420	425 430
Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala		
	435	440 445
Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys		
	450	455 460

<210> SEQ ID NO 75

<211> LENGTH: 443

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 75

Met Ala Leu Leu Ala Gly Gly Leu Ser Arg Gly Leu Gly Ser His Pro
1 5 10 15

Ala Ala Ala Gly Arg Asp Ala Val Val Phe Val Trp Leu Leu Ser
20 25 30

Thr Trp Cys Thr Ala Pro Ala Arg Ala Ile Gln Val Thr Val Ser Asn

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35					40					45					
Pro	Tyr	His	Val	Val	Ile	Leu	Phe	Gln	Pro	Val	Thr	Leu	Pro	Cys	Thr
50						55					60				
Tyr	Gln	Met	Thr	Ser	Thr	Pro	Thr	Gln	Pro	Ile	Val	Ile	Trp	Lys	Tyr
65					70					75					80
Lys	Ser	Phe	Cys	Arg	Asp	Arg	Ile	Ala	Asp	Ala	Phe	Ser	Pro	Ala	Ser
				85					90					95	
Val	Asp	Asn	Gln	Leu	Asn	Ala	Gln	Leu	Ala	Ala	Gly	Asn	Pro	Gly	Tyr
				100					105					110	
Asn	Pro	Tyr	Val	Glu	Cys	Gln	Asp	Ser	Val	Arg	Thr	Val	Arg	Val	Val
				115					120				125		
Ala	Thr	Lys	Gln	Gly	Asn	Ala	Val	Thr	Leu	Gly	Asp	Tyr	Tyr	Gln	Gly
	130					135					140				
Arg	Arg	Ile	Thr	Ile	Thr	Gly	Asn	Ala	Asp	Leu	Thr	Phe	Asp	Gln	Thr
145					150						155				160
Ala	Trp	Gly	Asp	Ser	Gly	Val	Tyr	Tyr	Cys	Ser	Val	Val	Ser	Ala	Gln
				165					170					175	
Asp	Leu	Gln	Gly	Asn	Asn	Glu	Ala	Tyr	Ala	Glu	Leu	Ile	Val	Leu	Gly
				180					185					190	
Arg	Thr	Ser	Gly	Val	Ala	Glu	Leu	Leu	Pro	Gly	Phe	Gln	Ala	Gly	Pro
				195					200				205		
Ile	Glu	Asp	Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro
	210					215						220			
Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro
225					230					235					240
Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr
				245						250					255
Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn
				260					265					270	
Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg
				275					280					285	
Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val
	290					295					300				
Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser
305					310					315					320
Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys
				325						330					335
Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp
				340					345					350	
Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe
	355						360						365		
Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu
	370					375					380				
Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe
385					390					395					400
Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly
				405						410					415
Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr
				420					425					430	
Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys					
	435							440							

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<211> LENGTH: 424
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 76

Met Ala Leu Leu Ala Gly Gly Leu Ser Arg Gly Leu Gly Ser His Pro
1      5      10      15

Ala Ala Ala Gly Arg Asp Ala Val Val Phe Val Trp Leu Leu Leu Ser
20      25      30

Thr Trp Cys Thr Ala Pro Ala Arg Ala Ile Gln Val Thr Val Ser Asn
35      40      45

Pro Tyr His Val Val Ile Leu Phe Gln Pro Val Thr Leu Pro Cys Thr
50      55      60

Tyr Gln Met Thr Ser Thr Pro Thr Gln Pro Ile Val Ile Trp Lys Tyr
65      70      75      80

Lys Ser Phe Cys Arg Asp Arg Ile Ala Asp Ala Phe Ser Pro Ala Ser
85      90      95

Val Asp Asn Gln Leu Asn Ala Gln Leu Ala Ala Gly Asn Pro Gly Tyr
100     105     110

Asn Pro Tyr Val Glu Cys Gln Asp Ser Val Arg Thr Val Arg Val Val
115     120     125

Ala Thr Lys Gln Gly Asn Ala Val Thr Leu Gly Asp Tyr Tyr Gln Gly
130     135     140

Arg Arg Ile Thr Ile Thr Gly Asn Ala Asp Leu Thr Phe Asp Gln Thr
145     150     155     160

Ala Trp Gly Asp Ser Gly Val Tyr Tyr Cys Ser Val Val Ser Ala Gln
165     170     175

Asp Leu Gln Gly Asn Asn Glu Ala Tyr Ala Glu Leu Ile Val Leu Asp
180     185     190

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
195     200     205

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
210     215     220

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
225     230     235     240

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
245     250     255

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
260     265     270

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
275     280     285

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
290     295     300

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
305     310     315     320

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
325     330     335

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
340     345     350

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
355     360     365

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
370     375     380

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Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
385 390 395 400

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
405 410 415

Ser Leu Ser Leu Ser Pro Gly Lys
420

<210> SEQ ID NO 77

<211> LENGTH: 765

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 77

Met Ala Leu Leu Ala Gly Gly Leu Ser Arg Gly Leu Gly Ser His Pro
1 5 10 15

Ala Ala Ala Gly Arg Asp Ala Val Val Phe Val Trp Leu Leu Ser
20 25 30

Thr Trp Cys Thr Ala Pro Ala Arg Ala Ile Gln Val Thr Val Ser Asn
35 40 45

Pro Tyr His Val Val Ile Leu Phe Gln Pro Val Thr Leu Pro Cys Thr
50 55 60

Tyr Gln Met Thr Ser Thr Pro Thr Gln Pro Ile Val Ile Trp Lys Tyr
65 70 75 80

Lys Ser Phe Cys Arg Asp Arg Ile Ala Asp Ala Phe Ser Pro Ala Ser
85 90 95

Val Asp Asn Gln Leu Asn Ala Gln Leu Ala Ala Gly Asn Pro Gly Tyr
100 105 110

Asn Pro Tyr Val Glu Cys Gln Asp Ser Val Arg Thr Val Arg Val Val
115 120 125

Ala Thr Lys Gln Gly Asn Ala Val Thr Leu Gly Asp Tyr Tyr Gln Gly
130 135 140

Arg Arg Ile Thr Ile Thr Gly Asn Ala Asp Leu Thr Phe Asp Gln Thr
145 150 155 160

Ala Trp Gly Asp Ser Gly Val Tyr Tyr Cys Ser Val Val Ser Ala Gln
165 170 175

Asp Leu Gln Gly Asn Asn Glu Ala Tyr Ala Glu Leu Ile Val Leu Val
180 185 190

Tyr Ala Ala Gly Lys Ala Ala Thr Ser Gly Val Pro Ser Ile Tyr Ala
195 200 205

Pro Ser Thr Tyr Ala His Leu Ser Pro Ala Lys Thr Pro Pro Pro Pro
210 215 220

Ala Met Ile Pro Met Gly Pro Ala Tyr Asn Gly Tyr Pro Gly Gly Tyr
225 230 235 240

Pro Gly Asp Val Asp Arg Ser Ser Ser Ala Gly Gly Gln Gly Ser Tyr
245 250 255

Val Pro Leu Leu Arg Asp Thr Asp Ser Ser Val Ala Ser Glu Val Arg
260 265 270

Ser Gly Tyr Arg Ile Gln Ala Ser Gln Gln Asp Asp Ser Met Arg Val
275 280 285

Leu Tyr Tyr Met Glu Lys Glu Leu Ala Asn Phe Asp Pro Ser Arg Pro
290 295 300

Gly Pro Pro Ser Gly Arg Val Glu Arg Ala Met Ser Glu Val Thr Ser
305 310 315 320

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Leu His Glu Asp Asp Trp Arg Ser Arg Pro Ser Arg Gly Pro Ala Leu
 325 330 335
 Thr Pro Ile Arg Asp Glu Glu Trp Gly Gly His Ser Pro Arg Ser Pro
 340 345 350
 Arg Gly Trp Asp Gln Glu Pro Ala Arg Glu Gln Ala Gly Gly Gly Trp
 355 360 365
 Arg Ala Arg Arg Pro Arg Ala Arg Ser Val Asp Ala Leu Asp Asp Leu
 370 375 380
 Thr Pro Pro Ser Thr Ala Glu Ser Gly Ser Arg Ser Pro Thr Ser Asn
 385 390 395 400
 Gly Gly Arg Ser Arg Ala Tyr Met Pro Pro Arg Ser Arg Ser Arg Asp
 405 410 415
 Asp Leu Tyr Asp Gln Asp Asp Ser Arg Asp Phe Pro Arg Ser Arg Asp
 420 425 430
 Pro His Tyr Asp Asp Phe Arg Ser Arg Glu Arg Pro Pro Ala Asp Pro
 435 440 445
 Arg Ser His His His Arg Thr Arg Asp Pro Arg Asp Asn Gly Ser Arg
 450 455 460
 Ser Gly Asp Leu Pro Tyr Asp Gly Arg Leu Leu Glu Glu Ala Val Arg
 465 470 475 480
 Lys Lys Gly Ser Glu Glu Arg Arg Arg Pro His Lys Glu Glu Glu Glu
 485 490 495
 Glu Ala Tyr Tyr Pro Pro Ala Pro Pro Tyr Ser Glu Thr Asp Ser
 500 505 510
 Gln Ala Ser Arg Glu Arg Arg Leu Lys Lys Asn Leu Ala Leu Ser Arg
 515 520 525
 Glu Ser Leu Val Val Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys
 530 535 540
 Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
 545 550 555 560
 Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
 565 570 575
 Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
 580 585 590
 Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
 595 600 605
 Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
 610 615 620
 Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
 625 630 635 640
 Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
 645 650 655
 Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
 660 665 670
 Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
 675 680 685
 Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
 690 695 700
 Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
 705 710 715 720
 Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
 725 730 735

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Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
740 745 750

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
755 760 765

<210> SEQ ID NO 78

<211> LENGTH: 764

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 78

Met Ala Leu Leu Ala Gly Gly Leu Ser Arg Gly Leu Gly Ser His Pro
1 5 10 15

Ala Ala Ala Gly Arg Asp Ala Val Val Phe Val Trp Leu Leu Leu Ser
20 25 30

Thr Trp Cys Thr Ala Pro Ala Arg Ala Ile Gln Val Thr Val Ser Asn
35 40 45

Pro Tyr His Val Val Ile Leu Phe Gln Pro Val Thr Leu Pro Cys Thr
50 55 60

Tyr Gln Met Thr Ser Thr Pro Thr Gln Pro Ile Val Ile Trp Lys Tyr
65 70 75 80

Lys Ser Phe Cys Arg Asp Arg Ile Ala Asp Ala Phe Ser Pro Ala Ser
85 90 95

Val Asp Asn Gln Leu Asn Ala Gln Leu Ala Ala Gly Asn Pro Gly Tyr
100 105 110

Asn Pro Tyr Val Glu Cys Gln Asp Ser Val Arg Thr Val Arg Val Val
115 120 125

Ala Thr Lys Gln Gly Asn Ala Val Thr Leu Gly Asp Tyr Tyr Gln Gly
130 135 140

Arg Arg Ile Thr Ile Thr Gly Asn Ala Asp Leu Thr Phe Asp Gln Thr
145 150 155 160

Ala Trp Gly Asp Ser Gly Val Tyr Tyr Cys Ser Val Val Ser Ala Gln
165 170 175

Asp Leu Gln Gly Asn Asn Glu Ala Tyr Ala Glu Leu Ile Val Leu Val
180 185 190

Tyr Ala Ala Gly Lys Ala Ala Thr Ser Gly Val Pro Ser Ile Tyr Ala
195 200 205

Pro Ser Thr Tyr Ala His Leu Ser Pro Ala Lys Thr Pro Pro Pro Pro
210 215 220

Ala Met Ile Pro Met Gly Pro Ala Tyr Asn Gly Tyr Pro Gly Gly Tyr
225 230 235 240

Pro Gly Asp Val Asp Arg Ser Ser Ser Ala Gly Gly Gln Gly Ser Tyr
245 250 255

Val Pro Leu Leu Arg Asp Thr Asp Ser Ser Val Ala Ser Val Arg Ser
260 265 270

Gly Tyr Arg Ile Gln Ala Ser Gln Gln Asp Asp Ser Met Arg Val Leu
275 280 285

Tyr Tyr Met Glu Lys Glu Leu Ala Asn Phe Asp Pro Ser Arg Pro Gly
290 295 300

Pro Pro Ser Gly Arg Val Glu Arg Ala Met Ser Glu Val Thr Ser Leu
305 310 315 320

His Glu Asp Asp Trp Arg Ser Arg Pro Ser Arg Gly Pro Ala Leu Thr
325 330 335

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Pro	Ile	Arg	Asp	Glu	Glu	Trp	Gly	Gly	His	Ser	Pro	Arg	Ser	Pro	Arg
			340					345					350		
Gly	Trp	Asp	Gln	Glu	Pro	Ala	Arg	Glu	Gln	Ala	Gly	Gly	Gly	Trp	Arg
		355					360					365			
Ala	Arg	Arg	Pro	Arg	Ala	Arg	Ser	Val	Asp	Ala	Leu	Asp	Asp	Leu	Thr
	370					375					380				
Pro	Pro	Ser	Thr	Ala	Glu	Ser	Gly	Ser	Arg	Ser	Pro	Thr	Ser	Asn	Gly
385					390					395					400
Gly	Arg	Ser	Arg	Ala	Tyr	Met	Pro	Pro	Arg	Ser	Arg	Ser	Arg	Asp	Asp
				405					410					415	
Leu	Tyr	Asp	Gln	Asp	Asp	Ser	Arg	Asp	Phe	Pro	Arg	Ser	Arg	Asp	Pro
			420					425					430		
His	Tyr	Asp	Asp	Phe	Arg	Ser	Arg	Glu	Arg	Pro	Pro	Ala	Asp	Pro	Arg
		435					440					445			
Ser	His	His	His	Arg	Thr	Arg	Asp	Pro	Arg	Asp	Asn	Gly	Ser	Arg	Ser
	450					455					460				
Gly	Asp	Leu	Pro	Tyr	Asp	Gly	Arg	Leu	Leu	Glu	Glu	Ala	Val	Arg	Lys
465					470					475					480
Lys	Gly	Ser	Glu	Glu	Arg	Arg	Arg	Pro	His	Lys	Glu	Glu	Glu	Glu	Glu
				485					490					495	
Ala	Tyr	Tyr	Pro	Pro	Ala	Pro	Pro	Pro	Tyr	Ser	Glu	Thr	Asp	Ser	Gln
			500					505					510		
Ala	Ser	Arg	Glu	Arg	Arg	Leu	Lys	Lys	Asn	Leu	Ala	Leu	Ser	Arg	Glu
		515					520					525			
Ser	Leu	Val	Val	Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro
	530					535					540				
Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe
545					550					555					560
Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val
				565					570					575	
Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe
			580					585					590		
Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro
		595					600					605			
Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr
	610					615					620				
Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val
625					630					635					640
Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala
				645					650					655	
Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg
			660					665					670		
Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly
		675					680					685			
Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro
	690					695					700				
Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser
705					710					715					720
Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln
				725				730						735	
Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His
			740					745					750		
Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys				

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755	760
<210> SEQ ID NO 79	
<211> LENGTH: 725	
<212> TYPE: PRT	
<213> ORGANISM: Artificial sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Synthetic polypeptide	
<400> SEQUENCE: 79	
Met Ala Leu Leu Ala Gly Gly Leu Ser Arg Gly Leu Gly Ser His Pro	
1 5 10 15	
Ala Ala Ala Gly Arg Asp Ala Val Val Phe Val Trp Leu Leu Leu Ser	
20 25 30	
Thr Trp Cys Thr Ala Pro Ala Arg Ala Ile Gln Val Thr Val Ser Asn	
35 40 45	
Pro Tyr His Val Val Ile Leu Phe Gln Pro Val Thr Leu Pro Cys Thr	
50 55 60	
Tyr Gln Met Thr Ser Thr Pro Thr Gln Pro Ile Val Ile Trp Lys Tyr	
65 70 75 80	
Lys Ser Phe Cys Arg Asp Arg Ile Ala Asp Ala Phe Ser Pro Ala Ser	
85 90 95	
Val Asp Asn Gln Leu Asn Ala Gln Leu Ala Ala Gly Asn Pro Gly Tyr	
100 105 110	
Asn Pro Tyr Val Glu Cys Gln Asp Ser Val Arg Thr Val Arg Val Val	
115 120 125	
Ala Thr Lys Gln Gly Asn Ala Val Thr Leu Gly Asp Tyr Tyr Gln Gly	
130 135 140	
Arg Arg Ile Thr Ile Thr Gly Met Tyr Ala Ala Gly Lys Ala Ala Thr	
145 150 155 160	
Ser Gly Val Pro Ser Ile Tyr Ala Pro Ser Thr Tyr Ala His Leu Ser	
165 170 175	
Pro Ala Lys Thr Pro Pro Pro Pro Ala Met Ile Pro Met Gly Pro Ala	
180 185 190	
Tyr Asn Gly Tyr Pro Gly Gly Tyr Pro Gly Asp Val Asp Arg Ser Ser	
195 200 205	
Ser Ala Gly Gly Gln Gly Ser Tyr Val Pro Leu Leu Arg Asp Thr Asp	
210 215 220	
Ser Ser Val Ala Ser Glu Val Arg Ser Gly Tyr Arg Ile Gln Ala Ser	
225 230 235 240	
Gln Gln Asp Asp Ser Met Arg Val Leu Tyr Tyr Met Glu Lys Glu Leu	
245 250 255	
Ala Asn Phe Asp Pro Ser Arg Pro Gly Pro Pro Ser Gly Arg Val Glu	
260 265 270	
Arg Ala Met Ser Glu Val Thr Ser Leu His Glu Asp Asp Trp Arg Ser	
275 280 285	
Arg Pro Ser Arg Gly Pro Ala Leu Thr Pro Ile Arg Asp Glu Glu Trp	
290 295 300	
Gly Gly His Ser Pro Arg Ser Pro Arg Gly Trp Asp Gln Glu Pro Ala	
305 310 315 320	
Arg Glu Gln Ala Gly Gly Trp Arg Ala Arg Arg Pro Arg Ala Arg	
325 330 335	
Ser Val Asp Ala Leu Asp Asp Leu Thr Pro Pro Ser Thr Ala Glu Ser	
340 345 350	
Gly Ser Arg Ser Pro Thr Ser Asn Gly Gly Arg Ser Arg Ala Tyr Met	

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355	360	365
Pro Pro Arg Ser Arg Ser Arg Asp Asp Leu Tyr Asp Gln Asp Asp Ser		
370	375	380
Arg Asp Phe Pro Arg Ser Arg Asp Pro His Tyr Asp Asp Phe Arg Ser		
385	390	395
Arg Glu Arg Pro Pro Ala Asp Pro Arg Ser His His His Arg Thr Arg		
	405	410
Asp Pro Arg Asp Asn Gly Ser Arg Ser Gly Asp Leu Pro Tyr Asp Gly		
	420	425
Arg Leu Leu Glu Glu Ala Val Arg Lys Lys Gly Ser Glu Glu Arg Arg		
	435	440
Arg Pro His Lys Glu Glu Glu Glu Glu Ala Tyr Tyr Pro Pro Ala Pro		
	450	455
Pro Pro Tyr Ser Glu Thr Asp Ser Gln Ala Ser Arg Glu Arg Arg Leu		
	465	470
Lys Lys Asn Leu Ala Leu Ser Arg Glu Ser Leu Val Val Glu Pro Lys		
	485	490
Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu		
	500	505
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr		
	515	520
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val		
	530	535
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val		
	545	550
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser		
	565	570
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu		
	580	585
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala		
	595	600
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro		
	610	615
Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln		
	625	630
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala		
	645	650
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr		
	660	665
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu		
	675	680
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser		
	690	695
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser		
	705	710
Leu Ser Pro Gly Lys		
	725	

<210> SEQ ID NO 80

<211> LENGTH: 784

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

-continued

<400> SEQUENCE: 80

Met	Ala	Leu	Leu	Ala	Gly	Gly	Leu	Ser	Arg	Gly	Leu	Gly	Ser	His	Pro
1				5					10					15	
Ala	Ala	Ala	Gly	Arg	Asp	Ala	Val	Val	Phe	Val	Trp	Leu	Leu	Leu	Ser
			20					25					30		
Thr	Trp	Cys	Thr	Ala	Pro	Ala	Arg	Ala	Ile	Gln	Val	Thr	Val	Ser	Asn
		35					40					45			
Pro	Tyr	His	Val	Val	Ile	Leu	Phe	Gln	Pro	Val	Thr	Leu	Pro	Cys	Thr
	50					55					60				
Tyr	Gln	Met	Thr	Ser	Thr	Pro	Thr	Gln	Pro	Ile	Val	Ile	Trp	Lys	Tyr
65					70					75					80
Lys	Ser	Phe	Cys	Arg	Asp	Arg	Ile	Ala	Asp	Ala	Phe	Ser	Pro	Ala	Ser
				85					90					95	
Val	Asp	Asn	Gln	Leu	Asn	Ala	Gln	Leu	Ala	Ala	Gly	Asn	Pro	Gly	Tyr
		100						105					110		
Asn	Pro	Tyr	Val	Glu	Cys	Gln	Asp	Ser	Val	Arg	Thr	Val	Arg	Val	Val
		115					120					125			
Ala	Thr	Lys	Gln	Gly	Asn	Ala	Val	Thr	Leu	Gly	Asp	Tyr	Tyr	Gln	Gly
	130					135					140				
Arg	Arg	Ile	Thr	Ile	Thr	Gly	Asn	Ala	Asp	Leu	Thr	Phe	Asp	Gln	Thr
145					150					155					160
Ala	Trp	Gly	Asp	Ser	Gly	Val	Tyr	Tyr	Cys	Ser	Val	Val	Ser	Ala	Gln
			165						170					175	
Asp	Leu	Gln	Gly	Asn	Asn	Glu	Ala	Tyr	Ala	Glu	Leu	Ile	Val	Leu	Gly
		180						185					190		
Arg	Thr	Ser	Gly	Val	Ala	Glu	Leu	Leu	Pro	Gly	Phe	Gln	Ala	Gly	Pro
	195						200					205			
Ile	Glu	Val	Tyr	Ala	Ala	Gly	Lys	Ala	Ala	Thr	Ser	Gly	Val	Pro	Ser
	210					215					220				
Ile	Tyr	Ala	Pro	Ser	Thr	Tyr	Ala	His	Leu	Ser	Pro	Ala	Lys	Thr	Pro
225					230					235					240
Pro	Pro	Pro	Ala	Met	Ile	Pro	Met	Gly	Pro	Ala	Tyr	Asn	Gly	Tyr	Pro
			245						250					255	
Gly	Gly	Tyr	Pro	Gly	Asp	Val	Asp	Arg	Ser	Ser	Ser	Ala	Gly	Gly	Gln
		260						265					270		
Gly	Ser	Tyr	Val	Pro	Leu	Leu	Arg	Asp	Thr	Asp	Ser	Ser	Val	Ala	Ser
	275						280					285			
Glu	Val	Arg	Ser	Gly	Tyr	Arg	Ile	Gln	Ala	Ser	Gln	Gln	Asp	Asp	Ser
	290					295					300				
Met	Arg	Val	Leu	Tyr	Tyr	Met	Glu	Lys	Glu	Leu	Ala	Asn	Phe	Asp	Pro
305					310					315					320
Ser	Arg	Pro	Gly	Pro	Pro	Ser	Gly	Arg	Val	Glu	Arg	Ala	Met	Ser	Glu
			325					330						335	
Val	Thr	Ser	Leu	His	Glu	Asp	Asp	Trp	Arg	Ser	Arg	Pro	Ser	Arg	Gly
		340						345					350		
Pro	Ala	Leu	Thr	Pro	Ile	Arg	Asp	Glu	Glu	Trp	Gly	Gly	His	Ser	Pro
	355						360					365			
Arg	Ser	Pro	Arg	Gly	Trp	Asp	Gln	Glu	Pro	Ala	Arg	Glu	Gln	Ala	Gly
	370					375					380				
Gly	Gly	Trp	Arg	Ala	Arg	Arg	Pro	Arg	Ala	Arg	Ser	Val	Asp	Ala	Leu
385					390					395					400
Asp	Asp	Leu	Thr	Pro	Pro	Ser	Thr	Ala	Glu	Ser	Gly	Ser	Arg	Ser	Pro
			405						410					415	

-continued

Thr	Ser	Asn	Gly	Gly	Arg	Ser	Arg	Ala	Tyr	Met	Pro	Pro	Arg	Ser	Arg	
			420					425					430			
Ser	Arg	Asp	Asp	Leu	Tyr	Asp	Gln	Asp	Asp	Ser	Arg	Asp	Phe	Pro	Arg	
		435					440					445				
Ser	Arg	Asp	Pro	His	Tyr	Asp	Asp	Phe	Arg	Ser	Arg	Glu	Arg	Pro	Pro	
		450				455					460					
Ala	Asp	Pro	Arg	Ser	His	His	His	Arg	Thr	Arg	Asp	Pro	Arg	Asp	Asn	
465					470					475					480	
Gly	Ser	Arg	Ser	Gly	Asp	Leu	Pro	Tyr	Asp	Gly	Arg	Leu	Leu	Glu	Glu	
			485						490					495		
Ala	Val	Arg	Lys	Lys	Gly	Ser	Glu	Glu	Arg	Arg	Arg	Pro	His	Lys	Glu	
			500					505					510			
Glu	Glu	Glu	Glu	Ala	Tyr	Tyr	Pro	Pro	Ala	Pro	Pro	Pro	Tyr	Ser	Glu	
		515					520					525				
Thr	Asp	Ser	Gln	Ala	Ser	Arg	Glu	Arg	Arg	Leu	Lys	Lys	Asn	Leu	Ala	
	530					535					540					
Leu	Ser	Arg	Glu	Ser	Leu	Val	Val	Glu	Pro	Lys	Ser	Ser	Asp	Lys	Thr	
545					550					555					560	
His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	
			565						570					575		
Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	
		580					585						590			
Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	
		595				600						605				
Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	
	610				615					620						
Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	
625					630					635					640	
Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	
		645						650					655			
Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	
		660					665						670			
Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	
	675					680					685					
Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	
	690				695					700						
Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	
705				710					715					720		
Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	
		725					730						735			
Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	
		740					745					750				
Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	
	755				760						765					
Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys	
	770				775						780					

<210> SEQ ID NO 81

<211> LENGTH: 106

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 81

-continued

Ala Asp Asn Met Gln Ala Ile Tyr Val Ala Leu Gly Glu Ala Val Glu
 1 5 10 15
 Leu Pro Cys Pro Ser Pro Pro Thr Leu His Gly Asp Glu His Leu Ser
 20 25 30
 Trp Phe Cys Ser Pro Ala Ala Gly Ser Phe Thr Thr Leu Val Ala Gln
 35 40 45
 Val Gln Val Gly Arg Pro Ala Pro Asp Pro Gly Lys Pro Gly Arg Glu
 50 55 60
 Ser Arg Leu Arg Leu Leu Gly Asn Tyr Ser Leu Trp Leu Glu Gly Ser
 65 70 75 80
 Lys Glu Glu Asp Ala Gly Arg Tyr Trp Cys Ala Val Leu Gly Gln His
 85 90 95
 His Asn Tyr Gln Asn Trp Arg Val Tyr Asp
 100 105

<210> SEQ ID NO 82
 <211> LENGTH: 89
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 82

Val Val Ile Gly Glu Val His Glu Asn Val Thr Leu His Cys Gly Asn
 1 5 10 15
 Ile Ser Gly Leu Arg Gly Gln Val Thr Trp Tyr Arg Asn Asn Ser Glu
 20 25 30
 Pro Val Phe Leu Leu Ser Ser Asn Ser Ser Leu Arg Pro Ala Glu Pro
 35 40 45
 Arg Phe Ser Leu Val Asp Ala Thr Ser Leu His Ile Glu Ser Leu Ser
 50 55 60
 Leu Gly Asp Glu Gly Ile Tyr Thr Cys Gln Glu Ile Leu Asn Val Thr
 65 70 75 80
 Gln Trp Phe Gln Val Trp Leu Gln Val
 85

<210> SEQ ID NO 83
 <211> LENGTH: 93
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 83

Pro Tyr Gln Ile Glu Val His Ile Val Ala Thr Gly Thr Leu Pro Asn
 1 5 10 15
 Gly Thr Leu Tyr Ala Ala Arg Gly Ser Gln Val Asp Phe Ser Cys Asn
 20 25 30
 Ser Ser Ser Arg Pro Pro Pro Val Val Glu Trp Trp Phe Gln Ala Leu
 35 40 45
 Asn Ser Ser Ser Glu Ser Phe Gly His Asn Leu Thr Val Asn Phe Phe
 50 55 60
 Ser Leu Leu Leu Ile Ser Pro Asn Leu Gln Gly Asn Tyr Thr Cys Leu
 65 70 75 80
 Ala Leu Asn Gln Leu Ser Lys Arg His Arg Lys Val Thr
 85 90

-continued

<210> SEQ ID NO 84
 <211> LENGTH: 87
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 84

```

Pro Pro Pro Ser Ala Pro Gln Cys Trp Ala Gln Met Ala Ser Gly Ser
1          5          10          15

Phe Met Leu Gln Leu Thr Cys Arg Trp Asp Gly Gly Tyr Pro Asp Pro
          20          25          30

Asp Phe Leu Trp Ile Glu Glu Pro Gly Gly Val Ile Val Gly Lys Ser
          35          40          45

Lys Leu Gly Val Glu Met Leu Ser Glu Ser Gln Leu Ser Asp Gly Lys
          50          55          60

Lys Phe Lys Cys Val Thr Ser His Ile Val Gly Pro Glu Ser Gly Ala
          65          70          75          80

Ser Cys Met Val Gln Ile Arg
          85
  
```

<210> SEQ ID NO 85
 <211> LENGTH: 94
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 85

```

Pro Ser Leu Leu Ser Glu Pro Met Lys Thr Cys Phe Thr Gly Gly Asn
1          5          10          15

Val Thr Leu Thr Cys Gln Val Ser Gly Ala Tyr Pro Pro Ala Lys Ile
          20          25          30

Leu Trp Leu Arg Asn Leu Thr Gln Pro Glu Val Ile Ile Gln Pro Ser
          35          40          45

Ser Arg His Leu Ile Thr Gln Asp Gly Gln Asn Ser Thr Leu Thr Ile
          50          55          60

His Asn Cys Ser Gln Asp Leu Asp Glu Gly Tyr Tyr Ile Cys Arg Ala
          65          70          75          80

Asp Ser Pro Val Gly Val Arg Glu Met Glu Ile Trp Leu Ser
          85          90
  
```

<210> SEQ ID NO 86
 <211> LENGTH: 185
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 86

```

Val Val Ile Gly Glu Val His Glu Asn Val Thr Leu His Cys Gly Asn
1          5          10          15

Ile Ser Gly Leu Arg Gly Gln Val Thr Trp Tyr Arg Asn Asn Ser Glu
          20          25          30

Pro Val Phe Leu Leu Ser Ser Asn Ser Ser Leu Arg Pro Ala Glu Pro
          35          40          45

Arg Phe Ser Leu Val Asp Ala Thr Ser Leu His Ile Glu Ser Leu Ser
          50          55          60

Leu Gly Asp Glu Gly Ile Tyr Thr Cys Gln Glu Ile Leu Asn Val Thr
          65          70          75          80
  
```

-continued

Gln Trp Phe Gln Val Trp Leu Gln Val Ala Ser Gly Pro Tyr Gln Ile
85 90 95

Glu Val His Ile Val Ala Thr Gly Thr Leu Pro Asn Gly Thr Leu Tyr
100 105 110

Ala Ala Arg Gly Ser Gln Val Asp Phe Ser Cys Asn Ser Ser Ser Arg
115 120 125

Pro Pro Pro Val Val Glu Trp Trp Phe Gln Ala Leu Asn Ser Ser Ser
130 135 140

Glu Ser Phe Gly His Asn Leu Thr Val Asn Phe Phe Ser Leu Leu Leu
145 150 155 160

Ile Ser Pro Asn Leu Gln Gly Asn Tyr Thr Cys Leu Ala Leu Asn Gln
165 170 175

Leu Ser Lys Arg His Arg Lys Val Thr
180 185

<210> SEQ ID NO 87
 <211> LENGTH: 279
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 87

Val Val Ile Gly Glu Val His Glu Asn Val Thr Leu His Cys Gly Asn
1 5 10 15

Ile Ser Gly Leu Arg Gly Gln Val Thr Trp Tyr Arg Asn Asn Ser Glu
20 25 30

Pro Val Phe Leu Leu Ser Ser Asn Ser Ser Leu Arg Pro Ala Glu Pro
35 40 45

Arg Phe Ser Leu Val Asp Ala Thr Ser Leu His Ile Glu Ser Leu Ser
50 55 60

Leu Gly Asp Glu Gly Ile Tyr Thr Cys Gln Glu Ile Leu Asn Val Thr
65 70 75 80

Gln Trp Phe Gln Val Trp Leu Gln Val Ala Ser Gly Pro Tyr Gln Ile
85 90 95

Glu Val His Ile Val Ala Thr Gly Thr Leu Pro Asn Gly Thr Leu Tyr
100 105 110

Ala Ala Arg Gly Ser Gln Val Asp Phe Ser Cys Asn Ser Ser Ser Arg
115 120 125

Pro Pro Pro Val Val Glu Trp Trp Phe Gln Ala Leu Asn Ser Ser Ser
130 135 140

Glu Ser Phe Gly His Asn Leu Thr Val Asn Phe Phe Ser Leu Leu Leu
145 150 155 160

Ile Ser Pro Asn Leu Gln Gly Asn Tyr Thr Cys Leu Ala Leu Asn Gln
165 170 175

Leu Ser Lys Arg His Arg Lys Val Thr Glu Leu Leu Val Tyr Tyr
180 185 190

Pro Pro Pro Ser Ala Pro Gln Cys Trp Ala Gln Met Ala Ser Gly Ser
195 200 205

Phe Met Leu Gln Leu Thr Cys Arg Trp Asp Gly Gly Tyr Pro Asp Pro
210 215 220

Asp Phe Leu Trp Ile Glu Glu Pro Gly Gly Val Ile Val Gly Lys Ser
225 230 235 240

Lys Leu Gly Val Glu Met Leu Ser Glu Ser Gln Leu Ser Asp Gly Lys
245 250 255

-continued

Lys Phe Lys Cys Val Thr Ser His Ile Val Gly Pro Glu Ser Gly Ala
 260 265 270

Ser Cys Met Val Gln Ile Arg
 275

<210> SEQ ID NO 88

<211> LENGTH: 374

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 88

Val Val Ile Gly Glu Val His Glu Asn Val Thr Leu His Cys Gly Asn
 1 5 10 15

Ile Ser Gly Leu Arg Gly Gln Val Thr Trp Tyr Arg Asn Asn Ser Glu
 20 25 30

Pro Val Phe Leu Leu Ser Ser Asn Ser Ser Leu Arg Pro Ala Glu Pro
 35 40 45

Arg Phe Ser Leu Val Asp Ala Thr Ser Leu His Ile Glu Ser Leu Ser
 50 55 60

Leu Gly Asp Glu Gly Ile Tyr Thr Cys Gln Glu Ile Leu Asn Val Thr
 65 70 75 80

Gln Trp Phe Gln Val Trp Leu Gln Val Ala Ser Gly Pro Tyr Gln Ile
 85 90 95

Glu Val His Ile Val Ala Thr Gly Thr Leu Pro Asn Gly Thr Leu Tyr
 100 105 110

Ala Ala Arg Gly Ser Gln Val Asp Phe Ser Cys Asn Ser Ser Ser Arg
 115 120 125

Pro Pro Pro Val Val Glu Trp Trp Phe Gln Ala Leu Asn Ser Ser Ser
 130 135 140

Glu Ser Phe Gly His Asn Leu Thr Val Asn Phe Phe Ser Leu Leu Leu
 145 150 155 160

Ile Ser Pro Asn Leu Gln Gly Asn Tyr Thr Cys Leu Ala Leu Asn Gln
 165 170 175

Leu Ser Lys Arg His Arg Lys Val Thr Thr Glu Leu Leu Val Tyr Tyr
 180 185 190

Pro Pro Pro Ser Ala Pro Gln Cys Trp Ala Gln Met Ala Ser Gly Ser
 195 200 205

Phe Met Leu Gln Leu Thr Cys Arg Trp Asp Gly Gly Tyr Pro Asp Pro
 210 215 220

Asp Phe Leu Trp Ile Glu Glu Pro Gly Gly Val Ile Val Gly Lys Ser
 225 230 235 240

Lys Leu Gly Val Glu Met Leu Ser Glu Ser Gln Leu Ser Asp Gly Lys
 245 250 255

Lys Phe Lys Cys Val Thr Ser His Ile Val Gly Pro Glu Ser Gly Ala
 260 265 270

Ser Cys Met Val Gln Ile Arg Gly Pro Ser Leu Leu Ser Glu Pro Met
 275 280 285

Lys Thr Cys Phe Thr Gly Gly Asn Val Thr Leu Thr Cys Gln Val Ser
 290 295 300

Gly Ala Tyr Pro Pro Ala Lys Ile Leu Trp Leu Arg Asn Leu Thr Gln
 305 310 315 320

Pro Glu Val Ile Ile Gln Pro Ser Ser Arg His Leu Ile Thr Gln Asp
 325 330 335

-continued

Gly Gln Asn Ser Thr Leu Thr Ile His Asn Cys Ser Gln Asp Leu Asp
340 345 350

Glu Gly Tyr Tyr Ile Cys Arg Ala Asp Ser Pro Val Gly Val Arg Glu
355 360 365

Met Glu Ile Trp Leu Ser
370

<210> SEQ ID NO 89

<211> LENGTH: 187

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 89

Pro Tyr Gln Ile Glu Val His Ile Val Ala Thr Gly Thr Leu Pro Asn
1 5 10 15

Gly Thr Leu Tyr Ala Ala Arg Gly Ser Gln Val Asp Phe Ser Cys Asn
20 25 30

Ser Ser Ser Arg Pro Pro Pro Val Val Glu Trp Trp Phe Gln Ala Leu
35 40 45

Asn Ser Ser Ser Glu Ser Phe Gly His Asn Leu Thr Val Asn Phe Phe
50 55 60

Ser Leu Leu Leu Ile Ser Pro Asn Leu Gln Gly Asn Tyr Thr Cys Leu
65 70 75 80

Ala Leu Asn Gln Leu Ser Lys Arg His Arg Lys Val Thr Thr Glu Leu
85 90 95

Leu Val Tyr Tyr Pro Pro Pro Ser Ala Pro Gln Cys Trp Ala Gln Met
100 105 110

Ala Ser Gly Ser Phe Met Leu Gln Leu Thr Cys Arg Trp Asp Gly Gly
115 120 125

Tyr Pro Asp Pro Asp Phe Leu Trp Ile Glu Glu Pro Gly Gly Val Ile
130 135 140

Val Gly Lys Ser Lys Leu Gly Val Glu Met Leu Ser Glu Ser Gln Leu
145 150 155 160

Ser Asp Gly Lys Lys Phe Lys Cys Val Thr Ser His Ile Val Gly Pro
165 170 175

Glu Ser Gly Ala Ser Cys Met Val Gln Ile Arg
180 185

<210> SEQ ID NO 90

<211> LENGTH: 282

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 90

Pro Tyr Gln Ile Glu Val His Ile Val Ala Thr Gly Thr Leu Pro Asn
1 5 10 15

Gly Thr Leu Tyr Ala Ala Arg Gly Ser Gln Val Asp Phe Ser Cys Asn
20 25 30

Ser Ser Ser Arg Pro Pro Pro Val Val Glu Trp Trp Phe Gln Ala Leu
35 40 45

Asn Ser Ser Ser Glu Ser Phe Gly His Asn Leu Thr Val Asn Phe Phe
50 55 60

Ser Leu Leu Leu Ile Ser Pro Asn Leu Gln Gly Asn Tyr Thr Cys Leu

-continued

65	70	75	80
Ala Leu Asn Gln Leu Ser Lys Arg His Arg Lys Val Thr Thr Glu Leu	85	90	95
Leu Val Tyr Tyr Pro Pro Pro Ser Ala Pro Gln Cys Trp Ala Gln Met	100	105	110
Ala Ser Gly Ser Phe Met Leu Gln Leu Thr Cys Arg Trp Asp Gly Gly	115	120	125
Tyr Pro Asp Pro Asp Phe Leu Trp Ile Glu Glu Pro Gly Gly Val Ile	130	135	140
Val Gly Lys Ser Lys Leu Gly Val Glu Met Leu Ser Glu Ser Gln Leu	145	150	155
Ser Asp Gly Lys Lys Phe Lys Cys Val Thr Ser His Ile Val Gly Pro	165	170	175
Glu Ser Gly Ala Ser Cys Met Val Gln Ile Arg Gly Pro Ser Leu Leu	180	185	190
Ser Glu Pro Met Lys Thr Cys Phe Thr Gly Gly Asn Val Thr Leu Thr	195	200	205
Cys Gln Val Ser Gly Ala Tyr Pro Pro Ala Lys Ile Leu Trp Leu Arg	210	215	220
Asn Leu Thr Gln Pro Glu Val Ile Ile Gln Pro Ser Ser Arg His Leu	225	230	235
Ile Thr Gln Asp Gly Gln Asn Ser Thr Leu Thr Ile His Asn Cys Ser	245	250	255
Gln Asp Leu Asp Glu Gly Tyr Tyr Ile Cys Arg Ala Asp Ser Pro Val	260	265	270
Gly Val Arg Glu Met Glu Ile Trp Leu Ser	275	280	

<210> SEQ ID NO 91

<211> LENGTH: 182

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 91

Pro Pro Pro Ser Ala Pro Gln Cys Trp Ala Gln Met Ala Ser Gly Ser	1	5	10	15
Phe Met Leu Gln Leu Thr Cys Arg Trp Asp Gly Gly Tyr Pro Asp Pro	20	25	30	
Asp Phe Leu Trp Ile Glu Glu Pro Gly Gly Val Ile Val Gly Lys Ser	35	40	45	
Lys Leu Gly Val Glu Met Leu Ser Glu Ser Gln Leu Ser Asp Gly Lys	50	55	60	
Lys Phe Lys Cys Val Thr Ser His Ile Val Gly Pro Glu Ser Gly Ala	65	70	75	80
Ser Cys Met Val Gln Ile Arg Gly Pro Ser Leu Leu Ser Glu Pro Met	85	90	95	
Lys Thr Cys Phe Thr Gly Gly Asn Val Thr Leu Thr Cys Gln Val Ser	100	105	110	
Gly Ala Tyr Pro Pro Ala Lys Ile Leu Trp Leu Arg Asn Leu Thr Gln	115	120	125	
Pro Glu Val Ile Ile Gln Pro Ser Ser Arg His Leu Ile Thr Gln Asp	130	135	140	
Gly Gln Asn Ser Thr Leu Thr Ile His Asn Cys Ser Gln Asp Leu Asp				

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145	150	155	160
Glu Gly Tyr Tyr Ile Cys Arg Ala Asp Ser Pro Val Gly Val Arg Glu			
	165	170	175
Met Glu Ile Trp Leu Ser			
	180		

<210> SEQ ID NO 92
 <211> LENGTH: 178
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 92

Val Val Ile Gly Glu Val His Glu Asn Val Thr Leu His Cys Gly Asn			
1	5	10	15
Ile Ser Gly Leu Arg Gly Gln Val Thr Trp Tyr Arg Asn Asn Ser Glu			
	20	25	30
Pro Val Phe Leu Leu Ser Ser Asn Ser Ser Leu Arg Pro Ala Glu Pro			
	35	40	45
Arg Phe Ser Leu Val Asp Ala Thr Ser Leu His Ile Glu Ser Leu Ser			
	50	55	60
Leu Gly Asp Glu Gly Ile Tyr Thr Cys Gln Glu Ile Leu Asn Val Thr			
	65	70	75
Gln Trp Phe Gln Val Trp Leu Gln Val Ala Asn Pro Pro Pro Ser Ala			
	85	90	95
Pro Gln Cys Trp Ala Gln Met Ala Ser Gly Ser Phe Met Leu Gln Leu			
	100	105	110
Thr Cys Arg Trp Asp Gly Gly Tyr Pro Asp Pro Asp Phe Leu Trp Ile			
	115	120	125
Glu Glu Pro Gly Gly Val Ile Val Gly Lys Ser Lys Leu Gly Val Glu			
	130	135	140
Met Leu Ser Glu Ser Gln Leu Ser Asp Gly Lys Lys Phe Lys Cys Val			
	145	150	155
Thr Ser His Ile Val Gly Pro Glu Ser Gly Ala Ser Cys Met Val Gln			
	165	170	175
Ile Arg			

<210> SEQ ID NO 93
 <211> LENGTH: 273
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 93

Val Val Ile Gly Glu Val His Glu Asn Val Thr Leu His Cys Gly Asn			
1	5	10	15
Ile Ser Gly Leu Arg Gly Gln Val Thr Trp Tyr Arg Asn Asn Ser Glu			
	20	25	30
Pro Val Phe Leu Leu Ser Ser Asn Ser Ser Leu Arg Pro Ala Glu Pro			
	35	40	45
Arg Phe Ser Leu Val Asp Ala Thr Ser Leu His Ile Glu Ser Leu Ser			
	50	55	60
Leu Gly Asp Glu Gly Ile Tyr Thr Cys Gln Glu Ile Leu Asn Val Thr			
	65	70	75
Gln Trp Phe Gln Val Trp Leu Gln Val Ala Asn Pro Pro Pro Ser Ala			

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85					90					95					
Pro	Gln	Cys	Trp	Ala	Gln	Met	Ala	Ser	Gly	Ser	Phe	Met	Leu	Gln	Leu
			100					105					110		
Thr	Cys	Arg	Trp	Asp	Gly	Gly	Tyr	Pro	Asp	Pro	Asp	Phe	Leu	Trp	Ile
			115				120					125			
Glu	Glu	Pro	Gly	Gly	Val	Ile	Val	Gly	Lys	Ser	Lys	Leu	Gly	Val	Glu
			130			135					140				
Met	Leu	Ser	Glu	Ser	Gln	Leu	Ser	Asp	Gly	Lys	Lys	Phe	Lys	Cys	Val
			145			150					155				160
Thr	Ser	His	Ile	Val	Gly	Pro	Glu	Ser	Gly	Ala	Ser	Cys	Met	Val	Gln
				165					170					175	
Ile	Arg	Gly	Pro	Ser	Leu	Leu	Ser	Glu	Pro	Met	Lys	Thr	Cys	Phe	Thr
				180				185					190		
Gly	Gly	Asn	Val	Thr	Leu	Thr	Cys	Gln	Val	Ser	Gly	Ala	Tyr	Pro	Pro
			195					200				205			
Ala	Lys	Ile	Leu	Trp	Leu	Arg	Asn	Leu	Thr	Gln	Pro	Glu	Val	Ile	Ile
			210			215					220				
Gln	Pro	Ser	Ser	Arg	His	Leu	Ile	Thr	Gln	Asp	Gly	Gln	Asn	Ser	Thr
				225		230					235				240
Leu	Thr	Ile	His	Asn	Cys	Ser	Gln	Asp	Leu	Asp	Glu	Gly	Tyr	Tyr	Ile
				245				250						255	
Cys	Arg	Ala	Asp	Ser	Pro	Val	Gly	Val	Arg	Glu	Met	Glu	Ile	Trp	Leu
			260					265					270		

Ser

<210> SEQ ID NO 94
 <211> LENGTH: 94
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 94

Pro	Gln	Ile	Asp	Gly	Gln	Thr	Trp	Ala	Glu	Arg	Ala	Leu	Arg	Glu	Asn
1				5					10					15	
Glu	Arg	His	Ala	Phe	Thr	Cys	Arg	Val	Ala	Gly	Gly	Pro	Gly	Thr	Pro
			20					25					30		
Arg	Leu	Ala	Trp	Tyr	Leu	Asp	Gly	Gln	Leu	Gln	Glu	Ala	Ser	Thr	Ser
			35				40					45			
Arg	Leu	Leu	Ser	Val	Gly	Gly	Glu	Ala	Phe	Ser	Gly	Gly	Thr	Ser	Thr
			50			55					60				
Phe	Thr	Val	Thr	Ala	His	Arg	Ala	Gln	His	Glu	Leu	Asn	Cys	Ser	Leu
			65		70					75					80
Gln	Asp	Pro	Arg	Ser	Gly	Arg	Ser	Ala	Asn	Ala	Ser	Val	Ile		
				85				90							

<210> SEQ ID NO 95
 <211> LENGTH: 145
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 95

Ile	Gln	Val	Thr	Val	Ser	Asn	Pro	Tyr	His	Val	Val	Ile	Leu	Phe	Gln
1				5					10					15	
Pro	Val	Thr	Leu	Pro	Cys	Thr	Tyr	Gln	Met	Thr	Ser	Thr	Pro	Thr	Gln

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20	25	30
Pro Ile Val Ile Trp Lys Tyr Lys Ser Phe Cys Arg Asp Arg Ile Ala		
35	40	45
Asp Ala Phe Ser Pro Ala Ser Val Asp Asn Gln Leu Asn Ala Gln Leu		
50	55	60
Ala Ala Gly Asn Pro Gly Tyr Asn Pro Tyr Val Glu Cys Gln Asp Ser		
65	70	75
Val Arg Thr Val Arg Val Val Ala Thr Lys Gln Gly Asn Ala Val Thr		
85	90	95
Leu Gly Asp Tyr Tyr Gln Gly Arg Arg Ile Thr Ile Thr Gly Asn Ala		
100	105	110
Asp Leu Thr Phe Asp Gln Thr Ala Trp Gly Asp Ser Gly Val Tyr Tyr		
115	120	125
Cys Ser Val Val Ser Ala Gln Asp Leu Gln Gly Asn Asn Glu Ala Tyr		
130	135	140
Ala		
145		

<210> SEQ ID NO 96
 <211> LENGTH: 72
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 96

Cys Pro Ser Pro Pro Thr Leu His Gly Asp Glu His Leu Ser Trp Phe
1 5 10 15
Cys Ser Pro Ala Ala Gly Ser Phe Thr Thr Leu Val Ala Gln Val Gln
20 25 30
Val Gly Arg Pro Ala Pro Asp Pro Gly Lys Pro Gly Arg Glu Ser Arg
35 40 45
Leu Arg Leu Leu Gly Asn Tyr Ser Leu Trp Leu Glu Gly Ser Lys Glu
50 55 60
Glu Asp Ala Gly Arg Tyr Trp Cys
65 70

<210> SEQ ID NO 97
 <211> LENGTH: 60
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 97

Cys Gly Asn Ile Ser Gly Leu Arg Gly Gln Val Thr Trp Tyr Arg Asn
1 5 10 15
Asn Ser Glu Pro Val Phe Leu Leu Ser Ser Asn Ser Ser Leu Arg Pro
20 25 30
Ala Glu Pro Arg Phe Ser Leu Val Asp Ala Thr Ser Leu His Ile Glu
35 40 45
Ser Leu Ser Leu Gly Asp Glu Gly Ile Tyr Thr Cys
50 55 60

<210> SEQ ID NO 98
 <211> LENGTH: 49
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:

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<210> SEQ ID NO 102
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 102

Cys Thr Tyr Gln Met Thr Ser Thr Pro Thr Gln Pro Ile Val Ile Trp
 1 5 10 15
 Lys Tyr Lys Ser Phe Cys Arg Asp Arg Ile Ala Asp Ala Phe Ser Pro
 20 25 30
 Ala Ser Val Asp Asn Gln Leu Asn Ala Gln Leu Ala Ala Gly Asn Pro
 35 40 45
 Gly Tyr Asn Pro Tyr Val Glu Cys Gln Asp Ser Val Arg Thr Val Arg
 50 55 60
 Val Val Ala Thr Lys Gln Gly Asn Ala Val Thr Leu Gly Asp Tyr Tyr
 65 70 75 80
 Gln Gly Arg Arg Ile Thr Ile Thr Gly Asn Ala Asp Leu Thr Phe Asp
 85 90 95
 Gln Thr Ala Trp Gly Asp Ser Gly Val Tyr Tyr Cys
 100 105

<210> SEQ ID NO 103
 <211> LENGTH: 2405
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 103

tccggcgtgg tgcgcaggcg cggtatcccc cctccccgc cagctcgacc ccggtgtggt 60
 gcgcaggcgc agtctgcgca gggactggcg ggactgcgcg gcggcaacag cagacatgtc 120
 ggggggtccg ggctgtgcgc ggctgtgtag cgtcggcgcg ctggcgctgg ccaaggcgtg 180
 gccaacagtg ttgcaaacag gaaccgaggg ttttcacttc actgttgatg ggaacaagag 240
 ggcatctgct aaagtttcag attccatttc tgctcagtat ccagtagtgg atcatgaatt 300
 tgatgcagtg gtggtaggcg ctggaggggc aggcttgcca gctgcatttg gcctttctga 360
 ggcagggttt aatacagcat gtgtttacaa gctgtttcct accaggtcac acactgttgc 420
 agcacaggga ggaatcaatg ctgctctggg gaacatggag gaggacaact ggagggtggca 480
 tttctacgac accgtgaagg gctccgactg gctgggggac caggatgcca tccactacat 540
 gacggagcag gccccgcgc ccgtggtcga gctagaaat tatggcatgc cgttttagcag 600
 aactgaagat ggaagatgtt atcagcgtgc atttggtgga cagagcctca agtttgga 660
 gggcgggcag gcccatcggt gctgctgtgt ggctgatcgg actggccact cgctattgca 720
 caccttatat ggaaggtctc tgcgatatga taccagctat tttgtggagt attttgcctt 780
 ggatctcctg atggagaatg gggagtgcgc tgggtgcatc gactgtgca tagaggacgg 840
 gtccatccat cgcataagag caaagaacac tggtgttgcc acaggaggct acgggcgcac 900
 ctacttcagc tgcacgtctg cccacaccag cactggcgac ggcacggcca tgatcaccag 960
 ggcaggcctt ccttgccagg acctagagtt tggtcagttc caccctacag gcatatatgg 1020
 tgctggttgt ctcattacgg aaggatgtcg tggagagga ggcattctca ttaacagtca 1080
 aggcgaaagg tttatggagc gatacgcccc tgctcggaag gacctggcgt ctagagatgt 1140
 ggtgtctcgg tccatgactc tggagatccg agaaggaaga ggctgtggcc ctgagaaaga 1200

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tcacgtctac ctgcagctgc accacctacc tccagagcag ctggccacgc gectgccttg	1260
catttcagag acagccatga tcttcgctgg cgtggacgtc acgaaggagc cgatccctgt	1320
cctccccacc gtgcattata acatgggcgg cattccccacc aactacaagg ggcaggtcct	1380
gaggcacgtg aatggccagg atcagattgt gcccggcctg tacgcctgtg gggaggccgc	1440
ctgtgcctcg gtacatgggtg ccaaccgcct cggggcaaac tcgctcttgg acctggttgt	1500
ctttggtcgg gcattgtgcc tgagcatcga agagtcatgc aggcctggag ataaagtccc	1560
tccaattaaa ccaaacgctg ggaagaatc tgtcatgaat cttgacaaat tgagatttgc	1620
tgatggaagc ataagaacat cggaactgcg actcagcatg cagaagtcaa tgcaaaatca	1680
tgctgccgtg ttccgtgtgg gaagcgtgtt gcaagaaggt tgtgggaaaa tcagcaagct	1740
ctatggagac ctaaaacacc tgaagcgtt cgaccgggga atggtctgga acacggacct	1800
ggtggagacc ctggagctgc agaacctgat gctgtgtgcg ctgcagacca tctacggagc	1860
agaggcacgg aaggagtcac ggggcccgcgca tgccagggaa gactacaagg tgcggattga	1920
tgagtacgat tactccaagc ccatccaggg gcaacagaag aagccctttg aggagcactg	1980
gaggaagcac accctgtcct atgtggacgt tggcactggg aaggtcactc tggaatatag	2040
acccgtgatc gacaaaactt tgaacgaggc tgactgtgcc accgtcccgc cagccattcg	2100
ctcctactga tgagacaaga tgtggtgatg acagaatcag cttttgtaat tatgtataat	2160
agctcatgca tgtgtccatg tcataactgt cttcatacgc ttctgcactc tggggaagaa	2220
ggagtacatt gaaggagat tggcacctag tggctgggag cttgccagga acccagtggc	2280
caggggagcgt ggcacttacc tttgtccctt gcttcattct tgtgagatga taaaactggg	2340
cacagctctt aaataaaata taaatgaaca aactttcttt tatttcctaaa aaaaaaaaaa	2400
aaaaa	2405

<210> SEQ ID NO 104
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 104

tggaacaag agggcatctg	20
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<210> SEQ ID NO 105
 <211> LENGTH: 22
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 105

ccaccactgc atcaaattca tg	22
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<210> SEQ ID NO 106
 <211> LENGTH: 86
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 106

tggaacaag agggcatctg ctaagtttc agattccatt tctgctcagt atccagtagt	60
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ggatcatgaa tttgatgcag tggtagg

86

<210> SEQ ID NO 107

<211> LENGTH: 1435

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 107

ggcggggcct gcttctctc agcttcaggc ggctgcgacg agccctcagg cgaacctctc 60

ggctttcccg cgcggcgccg cctcttctg cgcctccgcc tcctcctctg ctccgccacc 120

ggcttctctc tcctgagcag tcagcccgcg cgcggcgccg ctccgttatg gcgacccgca 180

gccctggcgt cgtgattagt gatgatgaac caggttatga ccttgattta tttgcatac 240

ctaatacatta tgctgaggat ttggaagggt tgtttattcc tcatggacta attatggaca 300

ggactgaacg tcttgctcga gatgtgatga aggagatggg aggccatcac attgtagccc 360

tctgtgtgct caaggggggc tataaattct ttgctgacct gctggattac atcaaagcac 420

tgaatagaaa tagtgataga tccattccta tgactgtaga ttttatcaga ctgaagagct 480

attgtaatga ccagtcacaa ggggacataa aagtaattgg tggagatgat ctctcaactt 540

taactggaaa gaatgtcttg attgtggaag atataattga cactggcaaa acaatgcaga 600

ctttgcttct cttggtcagg cagtataatc caaagatggt caaggctcga agcttgctgg 660

tgaaaaggac ccacgaagt gttggatata agccagactt tgttgattt gaaattccag 720

acaagtttgt ttaggatat gcccttgact ataatagaata cttcagggat ttgaatcatg 780

tttgtgtcat tagtgaaact ggaaaagcaa aatacaaagc ctaagatgag agttcaagtt 840

gagtttgaa acatctggag tcctattgac atcgccagta aaattatcaa tgttctagtt 900

ctgtggccat ctgcttagta gagctttttg catgtatctt ctaagaattt tatctgtttt 960

gtactttaga aatgtcagtt gctgcattcc taaactgttt atttgacta tgagcctata 1020

gactatcagt tccctttggg cggattgttg tttaacttgt aaatgaaaa attctcttaa 1080

accacagcac tattgagtga aacattgaac tcatatctgt aagaaataaa gagaagatat 1140

attagttttt taattggtat tttaattttt atatatgcag gaaagaatag aagtgtatga 1200

atattgttaa ttataccacc gtgtgttaga aaagtaagaa gcagtcaatt ttcacatcaa 1260

agacagcatc taagaagttt tgttctgtcc tggaattatt ttagtagtgt ttcagtaatg 1320

ttgactgtat tttccaactt gttcaaatta ttaccagtga atctttgtca gcagtccct 1380

tttaaatgca aatcaataaa ttcccaaaaa tttaaaaaaa aaaaaaaaaa aaaaa 1435

<210> SEQ ID NO 108

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 108

tgacactggc aaaacaatgc a

21

<210> SEQ ID NO 109

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

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<400> SEQUENCE: 109

ggtccttttc accagcaagc t	21
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<210> SEQ ID NO 110

<211> LENGTH: 94

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 110

tgacactggc aaaacaatgc agactttgct ttccttggtc aggcagtata atccaaagat	60
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ggtcaaggtc gcaagcttgc tggtagaaaag gacc	94
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<210> SEQ ID NO 111

<211> LENGTH: 2395

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 111

agaggcaggg gctggcctgg gatgcgcgcg cacctgcctt cgccccgccc cgcccgcacg	60
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aggggtggtg gccagggccc cgccccgcac gcctcgcttg aggcgggttc gctcagccca	120
---	-----

ggcgccccgc cccgcccccg ccgattaaat gggccggcgg ggctcagccc ccggaaacgg	180
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tcgtacactt cggggctgcg agcgcggagg gcgacgacga cgaagcgag acagcgctcat	240
---	-----

ggcagagcag gtggccctga gccggaccca ggtgtgcggg atcctgcggg aagagctttt	300
---	-----

ccaggcgcat gccttccatc agtcggatac acacatattc atcatcatgg gtgcacggg	360
--	-----

tgacctggcc aagaagaaga tctacccccc catctgggtg ctgttccggg atggccttct	420
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gccccaaaa accttcatcg tgggctatgc ccgttccgc ctcacagtgg ctgacatccg	480
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caaacagagt gagcccttct tcaaggccac cccagaggag aagctcaagc tggaggactt	540
---	-----

ctttgccgcg aactcctatg tggtctggca gtacgatgat gcagcctcct accagcgctt	600
---	-----

caacagccac atgaatgccc tccacctggg gtcacaggcc aaccgcctct tctacctggc	660
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cttgcccccg accgtctacg aggcctgcac caagaacatt cagagtcctt gcatgagcca	720
---	-----

gataggctgg aaccgcacga tcgtggagaa gcccttcggg agggacctgc agagctctga	780
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ccggtgtgac aaccacatct cctccctgtt ccgtgaggac cagatctacc gcatcgacca	840
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ctacctgggc aaggagatgg tgcagaacct catggtgctg agatttgcca acaggatctt	900
---	-----

cggccccatc tggaaccggg acaacatcgc ctgcgttata ctcacctca aggagccctt	960
--	-----

tggcactgag ggtgcggggg gctatttcga tgaatttggg atcatccggg acgtgatgca	1020
---	------

gaaccaccta ctgcagatgc tgtgtctggt ggccatggag aagcccgctt ccaccaactc	1080
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agatgacgtc cgtgatgaga aggtcaaggt gttgaaatgc atctcagagg tgcaggccaa	1140
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caatgtggtc ctgggcccagt acgtggggaa ccccgatgga gagggcgagg ccaccaaagg	1200
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gtacctggac gacccccagg tgcctcgagg gtccaccacc gccacttttg cagccgtcgt	1260
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cctctatgtg gagaatgaga ggtgggatgg ggtgcccttc atcctgcgct gcggcaaggc	1320
---	------

cctgaacgag cgcaaggccg aggtgaggct gcagttccat gatgtggccg gcgacatctt	1380
---	------

ccaccagcag tgcaagcgca acgagctggt gatccgcgtg cagcccaacg aggccgtgta	1440
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caccaagatg atgaccaaga agccgggcat gttcttcaac cccgaggagt cggagctgga	1500
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cctgacctac ggcaacagat acaagaacgt gaagctccct gacgectacg agcgctcat 1560
cctggacgtc ttctgcggga gccagatgca ctctgtgcgc agcgacgagc tccgtgaggc 1620
ctggcggtatt ttcaccccac tgctgcacca gattgagctg gagaagccca agcccatccc 1680
ctatatattat ggagcccgag gcccacgga ggacagagag ctgatgaaga gagtgggttt 1740
ccagtatgag ggacacctaca agtgggtgaa ccccacaag ctctgagccc tgggcaccca 1800
cctccacccc cgccacggcc accctccttc ccgcgcgcgc accccgagtc gggaggactc 1860
cgggaccatt gacctcagct gcacattcct ggccccgggc tctggccacc ctggcccgcc 1920
cctcgctgct gctactaccc gagcccagct acattcctca gctgccaaag actcgagacc 1980
atcctggccc ctccagaccc tgctgagcc caggagctga gtcacctcct ccactcactc 2040
cagcccaaca gaaggaagga ggaggcgccc cattcgtctg tcccagagct tattggccac 2100
tgggtctcac tcctgagtgg ggccaggggtg ggaggaggag acaaggggga ggaaaggggc 2160
gagcaccac gtgagagaat ctgcctgtgg ccttgcccgc cagcctcagt gccacttgac 2220
attccttgtc accagcaaca tctcgagccc cctggatgtc cctgtccca ccaactctgc 2280
actccatggc caccctgtgc caccgtagg cagcctctct gctataagaa aagcagacgc 2340
agcagctggg acccctccca acctcaatgc ctgccatta aatccgcaaa cagcc 2395

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<210> SEQ ID NO 112
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

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<400> SEQUENCE: 112

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gaggccgtca ccaagaacat 20

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<210> SEQ ID NO 113
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

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<400> SEQUENCE: 113

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ggacagccgg tcagagctc 19

```

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<210> SEQ ID NO 114
<211> LENGTH: 111
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

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<400> SEQUENCE: 114

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gaggccgtca ccaagaacat tcacgagtc tgcagagcc agataggctg gaaccgcac 60

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atcgtggaga agcccttcgg gagggacctg cagagctctg accggctgtc c 111

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<210> SEQ ID NO 115
<211> LENGTH: 1536
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

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<400> SEQUENCE: 115

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gtgacgcgag gctctgcgga gaccaggagt cagactgtag gacgacctg ggtccacgt 60

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gtccccggta ctgcgcggcc ggagcccccg gcttcccggg gccgggggac cttagcggca 120
cccacacaca gcctactttc caagcggagc catgtctggt aacggcaatg cggtcgcaac 180
ggcgggaagaa aacagcccaa agatgagagt gattcgcgtg ggtaccgcga agagccagct 240
tgctcgcata cagacggaca gtgtggtggc aacattgaaa gcctcgtagc ctggcctgca 300
gtttgaaatc attgctatgt ccaccacagg ggacaagatt cttgatactg cactctctaa 360
gattggagag aaaagcctgt ttaccaagga gcttgaacat gccctggaga agaatgaagt 420
ggacctgggt gttcactcct tgaaggacct gccactgtg cttcctcctg gcttcacct 480
cggagccatc tgcaagcggg aaaaccctca tgatgctgtt gtctttcacc caaaatttgt 540
tggaagacc ctgaaacccc tgccagagaa gagtgtggtg ggaaccagct ccctgcgaag 600
agcagcccag ctgcagagaa agttcccga tctggagttc aggagtattc ggggaaacct 660
caacaccggg cttcggaagc tggacgagca gcaggagttc agtgccatca tcctggcaac 720
agctggcctg cagcgcattg gctggcaca cgggtgggg cagatcctgc accctgagga 780
atgcatgtat gctgtggggc agggggcctt gggcgtggaa gtgcgagcca aggaccagga 840
catcttgat ctggtgggtg tgctgcacga tcccagact ctgcttcgt gcacgctga 900
aagggccttc ctgaggcacc tgaaggagg ctgcagtgtg ccagtagccg tgcatacagc 960
tatgaaggat gggcaactgt acctgactgg aggagtctg agtctagacg gctcagatag 1020
catacaagag accatgcagg ctaccatcca tgctccctgc cagcatgaag atggccctga 1080
ggatgaccca cagttggtag gcactactgc tcgtaacatt ccacgagggc ccagttggc 1140
tgcccagaac ttgggcatca gcctggccaa cttgttgctg agcaaggag ccaaaaacat 1200
cctggatgtt gcacggcagc ttaacgatgc ccattaactg gttgtgggg cacagatgcc 1260
tgggttgctg ctgtccagtg cctacatccc gggcctcagt gcccattct cactgctatc 1320
tggggagtga ttacccggg agactgaact gcagggttca agccttcag ggatttgct 1380
caccttgggg ccttgatgac tgccttgct cctcagtagt tgggggcttc atctcttag 1440
agaagtccaa gcaacagcct ttgaatgtaa ccaatctac taataaacca gttctgaag 1500
taaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaa 1536

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<210> SEQ ID NO 116
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

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<400> SEQUENCE: 116

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tgagagtgat tcgctggg 19

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<210> SEQ ID NO 117
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

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<400> SEQUENCE: 117

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ccagggtacg aggtttcaa t 21

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<210> SEQ ID NO 118
<211> LENGTH: 91
<212> TYPE: DNA

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<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 118

tgagagtgat tcgcgtgggt acccgcaaga gccagcttgc tcgcatacag acggacagtg 60
tgggtggcaac attgaaagcc tcgtaccctg g 91

<210> SEQ ID NO 119
<211> LENGTH: 748
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 119

gcagataatg ggaggagccg ggccccgagcg agctctttcc ttctgctgct gcggccgcag 60
ccatgagtat gctcaggctt cagaagaggc tcgcctctag tgctctccgc tgtggcaaga 120
agaaggtctg gttagacccc aatgagacca atgaaatcgc caatgccaac tcccgtcagc 180
agatccggaa gctcatcaaa gatgggctga tcatccgcaa gcctgtgacg gtccattccc 240
gggctcgatg ccggaaaaac accttgcccc gccggaaggg caggcacatg ggcataggta 300
agcgggaaggg tacagccaat gcccgaaatgc cagagaaggt cacatggatg aggagaaatga 360
ggatttttgcg ccggctgctc agaagatacc gtgaatctaa gaagatcgat cgccacatgt 420
atcacagcct gtacctgaag gtgaagggga atgtgttcaa aaacaagcgg attctcatgg 480
aacacatcca caagctgaag gcagacaagg cccgcaagaa gctcctggct gaccaggctg 540
aggccccgag gtctaagacc aaggaagcac gcaagcgcgc tgaagagcgc ctccaggcca 600
agaaggagga gatcatcaag actttatcca aggaggaaga gaccaagaaa taaaacctcc 660
cactttgtct gtacatactg gcctctgtga ttacatagat cagccattaa aataaaacaa 720
gccttaatat gcaaaaaaaaa aaaaaaaaa 748

<210> SEQ ID NO 120
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 120

tggcaagaag aaggtctggt tag 23

<210> SEQ ID NO 121
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 121

tgatcagccc atctttgatg ag 22

<210> SEQ ID NO 122
<211> LENGTH: 101
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 122

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tggcaagaag aaggtctggt tagaccccaa tgagaccaat gaaatcgcca atgccaactc	60
ccgtcagcag atccggaagc tcataaaga tgggctgac a	101

<210> SEQ ID NO 123
 <211> LENGTH: 186
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 123

ttcactgtca ctgcccatcg ggcccagcat gagctcaact gctctctgca ggaccccaga	60
agtggccgat cagccaacgc ctctgtcatc cttaatgtgc aattcaagcc agagattgcc	120
caagtgcgag ccaagtaacca ggaagctcag ggcccaggcc tctgtgtgt cctgtttgcc	180
ctggtg	186

<210> SEQ ID NO 124
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 124

ttcactgtca ctgcccatcg g	21
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<210> SEQ ID NO 125
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 125

caccagggca aacaggacaa c	21
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<210> SEQ ID NO 126
 <211> LENGTH: 1125
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 126

atggcgctgc ctccaggccc agccgccctc cggcacacac tgctgctcct gccagccctt	60
ctgagctcag gttgggggga gttggagcca caaatagatg gtcagacctg ggctgagcgg	120
gcacttcggg agaatgaacg ccacgccttc acctgccggg tggcaggggg gcctggcacc	180
cccagattgg cctggtatct ggatggacag ctgcaggagg ccagcacctc aagactgctg	240
agcgtgggag gggaggcctt ctctggaggc accagcacct tcaactgtcac tgcccatcgg	300
gcccagcatg agctcaactg ctctctgcag gaccccagaa gtggccgac agccaacgcc	360
tctgtcatcc ttaatgtgca attcaagcca gagattgccc aagtcggcgc caagtaccag	420
gaagctcagg gccaggcct cctggtgtgc ctgtttgccc tgggtgcgtgc caaccgcgcg	480
gccaatgtca cctggatcga ccaggatggg ccagtgactg tcaaacctc tgacttctcg	540
gtgctggatg cgcagaacta ccctggctc accaaccaca cgggtgcagct gcagtcgcg	600
agcctggcac acaacctctc ggtggtggcc accaatgacg tgggtgtcac cagtgcgtcg	660

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cttccagccc cagggcttct ggctaccggt gtggaagtgc cactgctggg cattgttgtg 720
gtgctggtggc ttgactggg caccctcgtg gggttcagca ccttggtggc ctgcctggtc 780
tgcagaaaag agaagaaaac caaaggcccc tcccggcacc catctctgat atcaagtgc 840
tccaacaacc taaaactcaa caacgtgcgc ctgccacggg agaacatgac cctcccgtcc 900
aaccttcagc tcaatgacct cactccagat tccagagcag tgaaccagc agaccggcag 960
atggctcaga acaacagccg gccagagctt ctggaccggg agcccgcgcg cctcctcacc 1020
agccaagggt tcattccgct cccagtgtg ggctatatct atcgagtgtc cagcgtgagc 1080
agtgatgaga tctggctcga ctacaagac gatgacgaca agtga 1125

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```

<210> SEQ ID NO 127
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

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<400> SEQUENCE: 127

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aaagctagcg ccaccatggc gctgcctcca ggcccag 37

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<210> SEQ ID NO 128
<211> LENGTH: 53
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

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<400> SEQUENCE: 128

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aaagaattct cacttgctgt catcgtcttt gtagtcgagc cagatctcat cac 53

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<210> SEQ ID NO 129
<211> LENGTH: 374
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide

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<400> SEQUENCE: 129

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Met Ala Leu Pro Pro Gly Pro Ala Ala Leu Arg His Thr Leu Leu Leu
1      5      10      15
Leu Pro Ala Leu Leu Ser Ser Gly Trp Gly Glu Leu Glu Pro Gln Ile
20     25     30
Asp Gly Gln Thr Trp Ala Glu Arg Ala Leu Arg Glu Asn Glu Arg His
35     40     45
Ala Phe Thr Cys Arg Val Ala Gly Gly Pro Gly Thr Pro Arg Leu Ala
50     55     60
Trp Tyr Leu Asp Gly Gln Leu Gln Glu Ala Ser Thr Ser Arg Leu Leu
65     70     75     80
Ser Val Gly Gly Glu Ala Phe Ser Gly Gly Thr Ser Thr Phe Thr Val
85     90     95
Thr Ala His Arg Ala Gln His Glu Leu Asn Cys Ser Leu Gln Asp Pro
100    105    110
Arg Ser Gly Arg Ser Ala Asn Ala Ser Val Ile Leu Asn Val Gln Phe
115    120    125
Lys Pro Glu Ile Ala Gln Val Gly Ala Lys Tyr Gln Glu Ala Gln Gly
130    135    140
Pro Gly Leu Leu Val Val Leu Phe Ala Leu Val Arg Ala Asn Pro Pro
145    150    155    160

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Ala Asn Val Thr Trp Ile Asp Gln Asp Gly Pro Val Thr Val Asn Thr
 165 170 175

Ser Asp Phe Leu Val Leu Asp Ala Gln Asn Tyr Pro Trp Leu Thr Asn
 180 185 190

His Thr Val Gln Leu Gln Leu Arg Ser Leu Ala His Asn Leu Ser Val
 195 200 205

Val Ala Thr Asn Asp Val Gly Val Thr Ser Ala Ser Leu Pro Ala Pro
 210 215 220

Gly Leu Leu Ala Thr Arg Val Glu Val Pro Leu Leu Gly Ile Val Val
 225 230 235 240

Ala Ala Gly Leu Ala Leu Gly Thr Leu Val Gly Phe Ser Thr Leu Val
 245 250 255

Ala Cys Leu Val Cys Arg Lys Glu Lys Lys Thr Lys Gly Pro Ser Arg
 260 265 270

His Pro Ser Leu Ile Ser Ser Asp Ser Asn Asn Leu Lys Leu Asn Asn
 275 280 285

Val Arg Leu Pro Arg Glu Asn Met Ser Leu Pro Ser Asn Leu Gln Leu
 290 295 300

Asn Asp Leu Thr Pro Asp Ser Arg Ala Val Lys Pro Ala Asp Arg Gln
 305 310 315 320

Met Ala Gln Asn Asn Ser Arg Pro Glu Leu Leu Asp Pro Glu Pro Gly
 325 330 335

Gly Leu Leu Thr Ser Gln Gly Phe Ile Arg Leu Pro Val Leu Gly Tyr
 340 345 350

Ile Tyr Arg Val Ser Ser Val Ser Ser Asp Glu Ile Trp Leu Asp Tyr
 355 360 365

Lys Asp Asp Asp Asp Lys
 370

<210> SEQ ID NO 130

<211> LENGTH: 1100

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 130

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atggcgctgc ctccaggccc agccgcccctc cggcacacac tgctgctcct gccagccctt    60
ctgagctcag gttgggggga gttggagcca caaatagatg gtcagacctg ggctgagcgg    120
gcacttcggg agaatgaacg ccacgccttc acctgccggg tggcaggggg gcctggcacc    180
cccagattgg cctggtatct ggatggacag ctgcaggagg ccagcacctc aagactgctg    240
agcgtgggag gggaggccct ctctggaggc accagcacct tcaactgtcac tgcccatcgg    300
gcccagcatg agctcaactg ctctctgcag gaccccagaa gtggccgacg agccaacgcc    360
tctgtcatcc ttaatgtgca attcaagcca gagattgccc aagtcggcgc caagtaccag    420
gaagctcagg gcccaggcct cctggttgtc ctgtttgccc tgggtgctgc caaccgccc    480
gccaatgtca cctggatoga ccaggatggg ccagtgactg tcaacacctc tgacttctg    540
gtgctggatg cgcagaacta cccctggctc accaaccaca cgggtgcagct gcagctccgc    600
agcctggcac acaacctctc ggtggtggcc accaatgacg tgggtgtcac cagtgcgtcg    660
cttcagccc cagggcttct ggctacccgg gtggaagtgc cactgctggg cattgttgtg    720
gtgctggggc ttgcactggg caccctcgtg gggttcagca ccttggtggc ctgcctggtc    780

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tgcagaaaag agaagaaaac caaaggcccc tcccggcacc catctctgat atcaagtgc	840
tccaacaacc taaaactcaa caacgtgcgc ctgccacggg agaacatgtc cctcccgctc	900
aaccttcagc tcaatgaact cactccagat tccagagcag tgaaaccagc agaccggcag	960
atggctcaga acaacagccg gccagagctt ctggacccgg agcccgccgg cctcctcacc	1020
agccaaggtt tcattccgct cccagtgtg ggctatatct atcgagtgtc cagcgtgagc	1080
agtgatgaga tctggctctg	1100

<210> SEQ ID NO 131
 <211> LENGTH: 29
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 131

aaagaattct cagagccaga tctcatcac	29
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<210> SEQ ID NO 132
 <211> LENGTH: 1476
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 132

atccagggtga ccgtgtccaa cccctaccac gtggtgatcc tcttcacgcc tgtgacctg	60
ccctgtacct accagatgac ctgcaccccc acgcaaccca tcgtcatctg gaagtacaag	120
tctttctgcc gggaccgcat cgccgatgcc ttctccccgg ccagcgtcga caaccagctc	180
aatgcccagc tggcagccgg gaaccacaggc tacaaccctt acgtcagtg ccaggacagc	240
gtgcgcaccg tcagggtcgt ggccaccaag cagggcaacg ctgtgacctt gggagattac	300
taccagggcc ggaggattac catcacccga aatgctgacc tgacctttga ccagacggcg	360
tgggggggaca gtggtgtgta ttactgtctc gtggtctcag ccaggacct ccagggggaa	420
aatgaggcct acgcagagct catcgtctt gtgtatgccg ccggcaaaag agccacctca	480
ggtgttccca gcatttatgc cccacgacc tatgcccacc tgtctccgc caagacccca	540
ccccaccag ctatgattcc catgggcctt gcttacaacg ggtaccctgg aggataacct	600
ggagacgttg acaggagtag ctacagctgtt ggccaaggct cctatgtacc cctgcttcgg	660
gacacggaca gcagtgtggc ctctgaagtc cgcagtggct acaggattca ggccagccag	720
caggacgact ccatgcgggt cctgtactac atggagaagg agctggccaa cttegacctt	780
tctcgacctg gccccccag tggccgtgtg gagcgggcca tgagtgaagt cacctccctc	840
cacgaggacg actggcgatc tcggccttcc cggggccctg ccctcaccac gatccgggat	900
gaggagtggg gtggccactc cccccggagt cccaggggat gggaccagga gcccgcagg	960
gagcaggcag gcgggggctg gcggggccagg cggccccggg cccgtctcgt ggacgcctg	1020
gacgacctca cccgcgcgag caccgcgag tcaggagaca ggtctccac gagtaatggt	1080
gggagaagcc gggcctacat gccccgcgg agccgcagcc gggacgacct ctatgaccaa	1140
gacgactcga gggacttccc acgtctcccg gacccccact acgacgacct cagggtctcg	1200
gagcgccctc ctgcgaccc caggtccac caccaccgta cccgggaccc tcgggacaa	1260
ggctccaggt ccggggacct cccctatgat gggcggtac tggaggaggc tgtgaggaa	1320
aaggggtcgg aggagaggag gagacccac aaggaggagg aggaagaggc ctactaccgc	1380

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cccgcgccgc ccccgctactc ggagaccgac tcgcaggcgt cccgagagcg cagggtcaag 1440

aagaacttgg ccctgagtcg ggaaagtta gtcgtc 1476

<210> SEQ ID NO 133

<211> LENGTH: 2201

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 133

cgggatttgg gtcgcggttc ttgtttgtgg atcgctgtga tcgtcacttg acaatgcaga 60

tcttcgtgaa gactctgact ggtaagacca tcacctcga gggtgagccc agtgacacca 120

tcgagaatgt caaggcaaag atccaagata aggaaggcat ccctcctgac cagcagaggc 180

tgatctttgc tggaaaacag ctggaagatg ggcgcaccct gtctgactac aacatccaga 240

aagagtccac cctgcacctg gtgctccgtc tcagagggtg gatgcaaac ttcgtgaaga 300

cactcactgg caagaccatc acccttgagg tggagcccag tgacaccatc gagaacgtca 360

aagcaaagat ccaggacaag gaaggcattc ctccctgacca gcagagggtg atctttgccg 420

gaaagcagct ggaagatggg cgcacctgt ctgactacaa catccagaaa gagtctaccc 480

tgcaacctgg gctccgtctc agagggtggga tgcagatctt cgtgaagacc ctgactggta 540

agaccatcac cctcgagggtg gagcccagtg acaccatcga gaatgtcaag gcaaagatcc 600

aagataagga aggcattcct cctgatcagc agaggttgat ctttgccgga aaacagctgg 660

aagatggtcg tacctgtctc gactacaaca tccagaaaga gtccacctg cacctggtac 720

tccgtctcag aggtgggatg caaatcttcg tgaagacct cactggcaag accatcacc 780

ttgaggtcga gccagtgac actatcgaga acgtcaaagc aaagatccaa gacaaggag 840

gcattcctcc tgaccagcag aggttgatct ttgccggaaa gcagctggaa gatgggagca 900

ccctgtctga ctacaacatc cagaaagagt ctacctgca cctggtgctc cgtctcagag 960

gtgggatgca gatcttcgtg aagacctga ctggtgaagc catcacctc gaagtggagc 1020

cgagtgcac cattgagaat gtcaaggcaa agatccaaga caagggaaggc atccctcctg 1080

accagcagag gttgatcttt gccggaaaac agctggaaga tggctgtacc ctgtctgact 1140

acaacatcca gaaagagtcc accttgccc tgggtgctccg tctcagagggt gggatgcaga 1200

tcttcgtgaa gacctgact ggtaagacca tcactctcga ggtggagccc agtgacacca 1260

ttgagaatgt caaggcaaag atccaagaca aggaaggcat ccctcctgat cagcagagggt 1320

tgatctttgc tgggaaaacag ctggaagatg gacgcacct gtctgactac aacatccaga 1380

aagagtccac cctgcacctg gtgctccgtc ttagagggtg gatgcagatc ttcgtgaaga 1440

ccctgactgg taagaccatc actctcgaag tggagccgag tgacaccatt gagaatgtca 1500

aggcaaagat ccaagacaag gaaggcatcc ctccctgacca gcagagggtg atctttgctg 1560

ggaaacagct ggaagatgga cgcacctgt ctgactacaa catccagaaa gagtccaccc 1620

tgcaacctgg gctccgtctc agagggtggga tgcagatctt cgtgaagacc ctgactggta 1680

agaccatcac tctcgaagtg gagccgagtg acaccattga gaatgtcaag gcaaagatcc 1740

aagacaagga aggcattcct cctgaccagc agaggttgat ctttgctggg aaacagctgg 1800

aagatggacg cacctgtctc gactacaaca tccagaaaga gtccacctg cacctggtgc 1860

tccgtctcag aggtgggatg cagatcttcg tgaagacct gactggtaag accatcacc 1920

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tcgaggtgga gcccagtgac accatcgaga atgtcaaggc aaagatccaa gataaggaag	1980
gcatccctcc tgatcagcag aggttgatct ttgctgggaa acagctggaa gatggacgca	2040
ccctgtctga ctacaacatc cagaaagagt ccactctgca cttggtcctg cgcttgaggg	2100
ggggtgtcta agtttccctt ttaaggttt caacaaattt cattgcactt tcctttcaat	2160
aaagttgttg cattcccaaa aaaaaaaaaa aaaaaaaaaa a	2201

<210> SEQ ID NO 134
 <211> LENGTH: 19
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 134

at ttgggtcg cggttcttg	19
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<210> SEQ ID NO 135
 <211> LENGTH: 21
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 135

tgcccttgaca ttctcgatgg t	21
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<210> SEQ ID NO 136
 <211> LENGTH: 133
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 136

at ttgggtcg cggttcttgt ttgtggatcg ctgtgatcgt cacttgacaa tgcagatctt	60
cgtgaagact ctgactggta agaccatcac cctcgagggt gagccagtg acaccatcga	120
gaatgtcaag gca	133

<210> SEQ ID NO 137
 <211> LENGTH: 182
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 137

gtcgacaacc agctcaatgc ccagctggca gccgggaacc caggctacaa cccctacgtc	60
gagtgccagg acagcgtgcg caccgtcagg gtcgtggcca ccaagcaggg caacgctgtg	120
accctgggag attactacca gggccggagg attaccatca ccggaaatgc tgacctgacc	180
tt	182

<210> SEQ ID NO 138
 <211> LENGTH: 20
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 138

gtcgacaacc agctcaatgc	20
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85								90				95				
Val	Asp	Asn	Gln	Leu	Asn	Ala	Gln	Leu	Ala	Ala	Gly	Asn	Pro	Gly	Tyr	
			100				105						110			
Asn	Pro	Tyr	Val	Glu	Cys	Gln	Asp	Ser	Val	Arg	Thr	Val	Arg	Val	Val	
			115				120				125					
Ala	Thr	Lys	Gln	Gly	Asn	Ala	Val	Thr	Leu	Gly	Asp	Tyr	Tyr	Gln	Gly	
			130	135						140						
Arg	Arg	Ile	Thr	Ile	Thr	Gly	Asn	Ala	Asp	Leu	Thr	Phe	Asp	Gln	Thr	
			145	150						155				160		
Ala	Trp	Gly	Asp	Ser	Gly	Val	Tyr	Tyr	Cys	Ser	Val	Val	Ser	Ala	Gln	
			165				170							175		
Asp	Leu	Gln	Gly	Asn	Asn	Glu	Ala	Tyr	Ala	Glu	Leu	Ile	Val	Leu	Gly	
			180				185							190		
Arg	Thr	Ser	Gly	Val	Ala	Glu	Leu	Leu	Pro	Gly	Phe	Gln	Ala	Gly	Pro	
			195				200				205					
Met	Glu	Asp	Trp	Leu	Phe	Val	Val	Val	Val	Cys	Leu	Ala	Ala	Phe	Leu	
			210	215						220						
Ile	Phe	Leu	Leu	Leu	Gly	Ile	Cys	Trp	Cys	Gln	Cys	Cys	Pro	His	Thr	
			225	230						235				240		
Cys	Cys	Cys	Tyr	Val	Arg	Cys	Pro	Cys	Cys	Pro	Asp	Lys	Cys	Cys	Cys	
			245				250							255		
Pro	Glu	Ala	Leu	Tyr	Ala	Ala	Gly	Lys	Ala	Ala	Thr	Ser	Gly	Val	Pro	
			260				265							270		
Ser	Ile	Tyr	Ala	Pro	Ser	Thr	Tyr	Ala	His	Leu	Ser	Pro	Ala	Lys	Thr	
			275				280				285					
Pro	Pro	Pro	Pro	Ala	Met	Ile	Pro	Met	Gly	Pro	Ala	Tyr	Asn	Gly	Tyr	
			290	295						300						
Pro	Gly	Gly	Tyr	Pro	Gly	Asp	Val	Asp	Arg	Ser	Ser	Ser	Ala	Gly	Gly	
			305	310						315				320		
Gln	Gly	Ser	Tyr	Val	Pro	Leu	Leu	Arg	Asp	Thr	Asp	Ser	Ser	Val	Ala	
			325				330							335		
Ser	Glu	Val	Arg	Ser	Gly	Tyr	Arg	Ile	Gln	Ala	Ser	Gln	Gln	Asp	Asp	
			340				345				350					
Ser	Met	Arg	Val	Leu	Tyr	Tyr	Met	Glu	Lys	Glu	Leu	Ala	Asn	Phe	Asp	
			355				360				365					
Pro	Ser	Arg	Pro	Gly	Pro	Pro	Ser	Gly	Arg	Val	Glu	Arg	Ala	Met	Ser	
			370	375						380						
Glu	Val	Thr	Ser	Leu	His	Glu	Asp	Asp	Trp	Arg	Ser	Arg	Pro	Ser	Arg	
			385	390						395				400		
Gly	Pro	Ala	Leu	Thr	Pro	Ile	Arg	Asp	Glu	Glu	Trp	Gly	Gly	His	Ser	
			405				410							415		
Pro	Arg	Ser	Pro	Arg	Gly	Trp	Asp	Gln	Glu	Pro	Ala	Arg	Glu	Gln	Ala	
			420				425				430					
Gly	Gly	Gly	Trp	Arg	Ala	Arg	Arg	Pro	Arg	Ala	Arg	Ser	Val	Asp	Ala	
			435				440				445					
Leu	Asp	Asp	Leu	Thr	Pro	Pro	Ser	Thr	Ala	Glu	Ser	Gly	Ser	Arg	Ser	
			450	455						460						
Pro	Thr	Ser	Asn	Gly	Gly	Arg	Ser	Arg	Ala	Tyr	Met	Pro	Pro	Arg	Ser	
			465	470						475				480		
Arg	Ser	Arg	Asp	Asp	Leu	Tyr	Asp	Gln	Asp	Asp	Ser	Arg	Asp	Phe	Pro	
			485				490				495					
Arg	Ser	Arg	Asp	Pro	His	Tyr	Asp	Asp	Phe	Arg	Ser	Arg	Glu	Arg	Pro	
			500	505						510						

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Pro Ala Asp Pro Arg Ser His His His Arg Thr Arg Asp Pro Arg Asp
515 520 525

Asn Gly Ser Arg Ser Gly Asp Leu Pro Tyr Asp Gly Arg Leu Leu Glu
530 535 540

Glu Ala Val Arg Lys Lys Gly Ser Glu Glu Arg Arg Arg Pro His Lys
545 550 555 560

Glu Glu Glu Glu Glu Ala Tyr Tyr Pro Pro Ala Pro Pro Pro Tyr Ser
565 570 575

Glu Thr Asp Ser Gln Ala Ser Arg Glu Arg Arg Leu Lys Lys Asn Leu
580 585 590

Ala Leu Ser Arg Glu Ser Leu Val Val
595 600

<210> SEQ ID NO 144
<211> LENGTH: 609
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 144

Met Ala Leu Leu Ala Gly Gly Leu Ser Arg Gly Leu Gly Ser His Pro
1 5 10 15

Ala Ala Ala Gly Arg Asp Ala Val Val Phe Val Trp Leu Leu Ser
20 25 30

Thr Trp Cys Thr Ala Pro Ala Arg Ala Ile Gln Val Thr Val Ser Asn
35 40 45

Pro Tyr His Val Val Ile Leu Phe Gln Pro Val Thr Leu Pro Cys Thr
50 55 60

Tyr Gln Met Thr Ser Thr Pro Thr Gln Pro Ile Val Ile Trp Lys Tyr
65 70 75 80

Lys Ser Phe Cys Arg Asp Arg Ile Ala Asp Ala Phe Ser Pro Ala Ser
85 90 95

Val Asp Asn Gln Leu Asn Ala Gln Leu Ala Ala Gly Asn Pro Gly Tyr
100 105 110

Asn Pro Tyr Val Glu Cys Gln Asp Ser Val Arg Thr Val Arg Val Val
115 120 125

Ala Thr Lys Gln Gly Asn Ala Val Thr Leu Gly Asp Tyr Tyr Gln Gly
130 135 140

Arg Arg Ile Thr Ile Thr Gly Asn Ala Asp Leu Thr Phe Asp Gln Thr
145 150 155 160

Ala Trp Gly Asp Ser Gly Val Tyr Tyr Cys Ser Val Val Ser Ala Gln
165 170 175

Asp Leu Gln Gly Asn Asn Glu Ala Tyr Ala Glu Leu Ile Val Leu Gly
180 185 190

Arg Thr Ser Gly Val Ala Glu Leu Leu Pro Gly Phe Gln Ala Gly Pro
195 200 205

Met Glu Asp Trp Leu Phe Val Val Val Val Cys Leu Ala Ala Phe Leu
210 215 220

Ile Phe Leu Leu Leu Gly Ile Cys Trp Cys Gln Cys Cys Pro His Thr
225 230 235 240

Cys Cys Cys Tyr Val Arg Cys Pro Cys Cys Pro Asp Lys Cys Cys Cys
245 250 255

Pro Glu Ala Leu Tyr Ala Ala Gly Lys Ala Ala Thr Ser Gly Val Pro
260 265 270

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Ser Ile Tyr Ala Pro Ser Thr Tyr Ala His Leu Ser Pro Ala Lys Thr
 275 280 285
 Pro Pro Pro Pro Ala Met Ile Pro Met Gly Pro Ala Tyr Asn Gly Tyr
 290 295 300
 Pro Gly Gly Tyr Pro Gly Asp Val Asp Arg Ser Ser Ser Ala Gly Gly
 305 310 315 320
 Gln Gly Ser Tyr Val Pro Leu Leu Arg Asp Thr Asp Ser Ser Val Ala
 325 330 335
 Ser Glu Val Arg Ser Gly Tyr Arg Ile Gln Ala Ser Gln Gln Asp Asp
 340 345 350
 Ser Met Arg Val Leu Tyr Tyr Met Glu Lys Glu Leu Ala Asn Phe Asp
 355 360 365
 Pro Ser Arg Pro Gly Pro Pro Ser Gly Arg Val Glu Arg Ala Met Ser
 370 375 380
 Glu Val Thr Ser Leu His Glu Asp Asp Trp Arg Ser Arg Pro Ser Arg
 385 390 395 400
 Gly Pro Ala Leu Thr Pro Ile Arg Asp Glu Glu Trp Gly Gly His Ser
 405 410 415
 Pro Arg Ser Pro Arg Gly Trp Asp Gln Glu Pro Ala Arg Glu Gln Ala
 420 425 430
 Gly Gly Gly Trp Arg Ala Arg Arg Pro Arg Ala Arg Ser Val Asp Ala
 435 440 445
 Leu Asp Asp Leu Thr Pro Pro Ser Thr Ala Glu Ser Gly Ser Arg Ser
 450 455 460
 Pro Thr Ser Asn Gly Gly Arg Ser Arg Ala Tyr Met Pro Pro Arg Ser
 465 470 475 480
 Arg Ser Arg Asp Asp Leu Tyr Asp Gln Asp Asp Ser Arg Asp Phe Pro
 485 490 495
 Arg Ser Arg Asp Pro His Tyr Asp Asp Phe Arg Ser Arg Glu Arg Pro
 500 505 510
 Pro Ala Asp Pro Arg Ser His His His Arg Thr Arg Asp Pro Arg Asp
 515 520 525
 Asn Gly Ser Arg Ser Gly Asp Leu Pro Tyr Asp Gly Arg Leu Leu Glu
 530 535 540
 Glu Ala Val Arg Lys Lys Gly Ser Glu Glu Arg Arg Arg Pro His Lys
 545 550 555 560
 Glu Glu Glu Glu Glu Ala Tyr Tyr Pro Pro Ala Pro Pro Pro Tyr Ser
 565 570 575
 Glu Thr Asp Ser Gln Ala Ser Arg Glu Arg Arg Leu Lys Lys Asn Leu
 580 585 590
 Ala Leu Ser Arg Glu Ser Leu Val Val Asp Tyr Lys Asp Asp Asp Asp
 595 600 605

Lys

<210> SEQ ID NO 145

<211> LENGTH: 1806

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 145

atggcgctgt tggccggcgg gctctccaga gggctgggct cccaccggc cgccgcaggc 60

cgggacgcgg tcgtcttcgt gtggcttctg cttagcacct ggtgcacagc tcctgccaga 120

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gccatccagg	tgaccgtgtc	caaccctac	cacgtggtga	tccttttcca	gcctgtgacc	180
ctgccctgta	cctaccagat	gacctcgacc	cccacgcaac	ccatcgteat	ctggaagtac	240
aagtctttct	gccgggaccg	catcgccgat	gcctttctcc	cggccagcgt	cgacaaccag	300
ctcaatgccc	agctggcagc	cgggaaccca	ggctacaacc	cctacgtcga	gtgccaggac	360
agcgtgcgca	ccgtcagggc	cgtggccacc	aagcagggca	acgtgtgtac	cctgggagat	420
tactaccagg	gccggaggat	taccatcacc	ggaaatgctg	acctgacctt	tgaccagacg	480
gcgtgggggg	acagtgtgtg	gtattactgc	tcctgtgtct	cagcccagga	cctccagggg	540
aacaatgagg	cctacgcaga	gctcatcgtc	cttgggagga	cctcaggggt	ggctgagctc	600
ttacctgggt	ttcaggcggg	gcccatggaa	gactggctct	tcgtgggtgt	ggtagcctg	660
gctgccttcc	tcctcttctc	cctcctgggc	atctgctggg	gccagtgtgt	cccgcacact	720
tgctgctgct	acgtcagggt	cccctgctgc	ccagacaagt	gctgctgccc	cgaggccctg	780
tatgccgccc	gcaaacgagc	cacctcaggt	gttcccagca	tttatgcccc	cagcacctat	840
gcccacctgt	ctccccccaa	gacccacccc	ccaccageta	tgatttccat	gggcccctgcc	900
tacaacgggt	accctggagg	ataccctgga	gacgttgaca	ggagtagctc	agctggtggc	960
caaggctcct	atgtaccctc	gcttcggggc	acggacagca	gtgtggcctc	tgaagtcgc	1020
agtggctaca	ggattcaggc	cagccagcag	gacgactcca	tgccgggtct	gtactacatg	1080
gagaaggagc	tggccaactt	cgacccttct	cgacctggcc	ccccagtggt	ccgtgtggag	1140
cgggcatga	gtgaagtcac	ctccctccac	gaggacgact	ggcgatctcg	gccttcccgg	1200
ggccctgccc	tcaccccgat	ccgggatgag	gagtggggtg	gccactcccc	ccggagtccc	1260
aggggatggg	accaggagcc	cgccagggag	caggcaggcg	gggctggcgg	ggccaggcgg	1320
ccccgggccc	gctcctggga	cgccctggac	gacctcacc	cgccgagcac	cgccgagtca	1380
gggagcaggt	ctcccacgag	taatggtggg	agaagccggg	cctacatgcc	cccgcgagac	1440
cgcagccggg	acgacctcta	tgaccaagac	gactcgaggg	acttcccacg	ctcccgggac	1500
ccccactacg	acgacttcag	gtctcggggg	cgccctcctg	ccgaccccag	gtcccaccac	1560
caccgtaccc	gggacctctg	ggacaacggc	tccagggtccg	gggacctccc	ctatgatggg	1620
cggctactgg	aggaggctgt	gaggaagaag	gggtcggagg	agaggaggag	acccacacaag	1680
gaggaggagg	aaggaggcta	ctacccgccc	cgcccgcccc	cgtactcgga	gaccgactcg	1740
caggcgctcc	gagagcgag	gctcaagaag	aacttgcccc	tgagtgggga	aagtttagtc	1800
gtctga						1806

<210> SEQ ID NO 146

<211> LENGTH: 1830

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 146

atggcgctgt	tggccggcgg	gctctccaga	gggctgggct	ccccccggc	cgccgcaggc	60
cgggacgcgg	tcgtcttctg	gtggcttctg	cttagcacct	ggtgcacagc	tcctgccaga	120
gccatccagg	tgaccgtgtc	caaccctac	cacgtggtga	tccttttcca	gcctgtgacc	180
ctgccctgta	cctaccagat	gacctcgacc	cccacgcaac	ccatcgteat	ctggaagtac	240
aagtctttct	gccgggaccg	catcgccgat	gcctttctcc	cggccagcgt	cgacaaccag	300

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ctcaatgccc agctggcagc cggaaccca ggctacaacc cctacgtcga gtgccaggac	360
agcgtgcgca cgcgcagggt cgtggccacc aagcagggca acgctgtgac cctgggagat	420
tactaccagg gccggaggat taccatcacc ggaaatgctg acctgacctt tgaccagacg	480
gcgtgggggg acagtgggtg gtattactgc tccgtgggtc cagcccagga cctccagggg	540
aacaatgagg cctacgcaga gctcatcgtc cttggggagga cctcaggggt ggctgagctc	600
ttacctggtt ttcaggcggg gcccatggaa gactggctct tcgtgggtgt ggtatgctg	660
gctgccttcc tcctcttctt cctcctgggc atctgctggt gccagtgtg cccgcacact	720
tgctgctgct acgtcagggt cccctgctgc ccagacaagt gctgctgccc cgaggccctg	780
tatgccgccc gcaaagcagc cacctcaggt gtteccagca tttatgccc cagcacctat	840
gcccacctgt ctcccgcga gacccacccc ccaccagcta tgattcccat ggccctgcc	900
tacaacgggt accctggagg ataccctgga gacgttgaca ggagtagctc agctggtggc	960
caaggctcct atgtaccctt gcttcgggac acggacagca gtgtggcctc tgaagtccgc	1020
agtggctaca ggattcaggc cagccagcag gacgactcca tgcgggtcct gtactacatg	1080
gagaaggagc tggccaactt cgacccttct cgacctggcc ccccagtggt ccgtgtggag	1140
cgggcatga gtgaagtcc ctcctccac gaggacgact ggcgatctcg gccttcccg	1200
ggccctgccc tcaccccgat ccgggatgag gagtggggtg gccactcccc ccggagtccc	1260
aggggatggg accaggagcc cgcaggagg caggcaggcg ggggctggcg ggccaggcgg	1320
ccccgggccc gctccgtgga cgcctcggac gacctcacc cgccgagcac cgccagtc	1380
gggagcaggt ctcccacgag taatggtggg agaagccggg cctacatgcc ccgcggagc	1440
cgcagccggg acgacctcta tgaccaagac gactcgaggg acttcccacg ctcccgggac	1500
ccccactacg acgacttcag gtctcgggag cgcctcctg ccgaccccag gtcccaccac	1560
caccgtaccc gggaccctcg ggacaacggc tccagggtccg gggacctccc ctatgatggg	1620
cggctactgg aggaggctgt gaggaagaag gggtcggagg agaggaggag accccacaag	1680
gaggaggagg aaggaggcta ctaccgccc gcgcgcccc cgtactcgga gaccgactcg	1740
caggcgtccc gagagcgcag gctcaagaag aacttggccc tgagtcggga aagtttagtc	1800
gtcgactaca aagacgatga cgacaagtga	1830

<210> SEQ ID NO 147
 <211> LENGTH: 32
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 147

tatgctagcg ccaccatggc gctgttgccc gg	32
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<210> SEQ ID NO 148
 <211> LENGTH: 25
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 148

tcagacgact aaactttccc gactc	25
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<210> SEQ ID NO 149
 <211> LENGTH: 20

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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 149

caggtaagag ctcagccacc                20

<210> SEQ ID NO 150
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 150

ggtggtgag ctcttacctg                20

<210> SEQ ID NO 151
<211> LENGTH: 58
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 151

gatggatcct cacttgctgt catcgtcttt gtagtcgacg actaaacttt cccgactc    58

<210> SEQ ID NO 152
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 152

gatggatcct cagacgacta aactttcccg actc                34

<210> SEQ ID NO 153
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 153

Asp Tyr Lys Asp Asp Asp Asp Lys
1      5

<210> SEQ ID NO 154
<211> LENGTH: 1950
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 154

atgcaacagg acggacttgg agtagggaca aggaacggaa gtgggaaggg gaggagcgtg    60
caccctcctt ggccttggtg cgcgcgcgcg cccctaaggt actttggaag ggacgcgcgg    120
gccagacgcg ccagacgggc cgcgatggcg ctgttgggcg gcgggctctc cagagggctg    180
ggctcccacc cgccgcgcgc aggccgggac ggggtcgtct tcgtgtggct tctgcttagc    240
acctggtgca cagctcctgc cagggccatc caggtgaccg tgtccaacct ctaccacgtg    300
gtgatcctct tccagcctgt gaccctgccc tgtacctacc agatgacctc gacccccacg    360

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caacccatcg tcatctggaa gtacaagtct ttctgccggg accgcacgc cgatgccttc	420
tccccggcca gcgtcgacaa ccagctcaat gccagctgg cagccgggaa cccaggctac	480
aacccctacg tcgagtgcc ggacagcgtg cgcaccgtca gggtcgtggc caccaagcag	540
ggcaacgctg tgacctggg agattactac cagggccgga ggattaccat caccggaaat	600
gctgacctga cctttgacca gacggcgtgg ggggacagtg gtgtgtatta ctgctccgtg	660
gtctcagccc aggacctcca ggggaacaat gaggcctacg cagagctcat cgtccttggg	720
aggacctcag gggtggtga gctcttacct ggttttcagg cggggcccat agaagactgg	780
ctcttcgtgg ttgtggtatg cctggctgcc ttctctatct tctctctct gggcatctgc	840
tggtgccagt gctccccga cacttgctgc tgctacgtca ggtgccctg ctgccagac	900
aagtgtgtct gccccgaggc cctgtatgcc gccggcaaag cagccacctc agtggttccc	960
agcatttatg cccccagcac ctatgccac ctgtctcccg ccaagacccc acccccacca	1020
gctatgattc ccatgggccc tgccataaac gggtagccctg gaggataccc tggagacgtt	1080
gacaggagta gctcagctgg tgccaaggc tctatgtac cctgcttcg ggacacggac	1140
agcagtgtgg cctctgaagt ccgcagtggc tacaggattc aggccagcca gcaggacgac	1200
tccatgcggg tcctgtacta catggagaag gagctggcca acttcgaccc ttctcgacct	1260
ggccccccca gtggcgtgt ggagcgggcc atgagtgaag tcacctcct ccacgaggac	1320
gactggcgat ctccgccttc ccggggccct gccctcacc cgcctccgga tgaggagtgg	1380
ggtggccact ccccccgag tcccagggga tgggaccagg agcccgcag ggagcaggca	1440
ggcgggggct ggcggggcag gcggccccg gcccgctccg tggacgccct ggacgacctc	1500
accccgccga gcaccgccga gtcagggagc aggtctccca cgagtaatgg tgggagaagc	1560
cgggcctaca tgcccccgcg gagccgcagc cgggacgacc tctatgacca agacgactcg	1620
agggaacttc cacgtcccg ggacccccac tacgacgact tcagggtctg ggagcgccct	1680
cctgccgacc ccaggctcca ccaccaccgt acccgggacc ctccggacaa cggtccagg	1740
tccggggacc tcccctatga tggggcgcta ctggaggagg ctgtgaggaa gaaggggtcg	1800
gaggagagga ggagacccca caaggaggag gaggaagagg cctactacc gcccgcgccg	1860
ccccgtact cggagaccga ctgcaggcg tcccagagc gcaggctcaa gaagaacttg	1920
gccctgagtc gggaaagttt agtcgtctga	1950

<210> SEQ ID NO 155

<211> LENGTH: 1356

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 155

atccaggatga ccgtgtccaa cccctaccac gtggtgatec tcttcagcc tgtgacctg	60
ccctgtacct accagatgac ctgcaccccc acgcaaccca tcgtcatctg gaagtacaag	120
tctttctgcc gggaccgcat cgcgatgcc ttctccccg ccagcgtcga caaccagctc	180
aatgcccagc tggcagccg gaaccaggc tacaaccct acgtcagtg ccaggacagc	240
gtgcgcaccg tcagggtcgt ggccaccaag cagggaacg ctgtgacctt gggagattac	300
taccagggcc ggaggattac catcacgga atgtatgcc cggcaaaag agccacctca	360
ggtgttccca gcatttatgc cccagcacc tatgccacc tgtctccgc caagacccca	420

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ccccaccag ctatgattcc catgggccct gcctacaacg ggtaccctgg aggataccct 480
ggagacgttg acaggagtag ctcagctggt ggccaaggct cctatgtacc cctgcttcgg 540
gacacggaca gcagtgtggc cttctgaagtc cgcagtggct acaggattca ggccagccag 600
caggacgact ccatgcgggt cctgtactac atggagaagg agctggccaa cttegaccct 660
tctcgacctg gcccccccag tggccgtgtg gagcggggcca tgagtgaagt cacctccctc 720
cacgaggacg actggcgatc tcggccttcc cggggccctg ccctcacccc gatccgggat 780
gaggagtggg gtggccactc cccccggagt ccagggggat gggaccagga gcccgccagg 840
gagcaggcag gcgggggctg gcggggccagg cggccccggg ccgctccgt ggacgccctg 900
gacgacctca ccccgccgag caccgccgag tcaggagaca ggtctccac gagtaatggt 960
gggagaagcc gggcctacat gcccccgcg agccgcagcc gggacgacct ctatgaccaa 1020
gacgactcga gggacttccc acgctcccgg gacccccact acgacgactt cagggtctcg 1080
gagcgccctc ctgccgacct cagggtccac caccaccgta cccgggacct tcgggacaac 1140
ggctccaggt ccggggacct ccctatgat gggcggtac tggaggaggc tgtgaggaag 1200
aaggggtcgg aggagaggag gagacccac aaggaggagg aggaagaggc ctactacccg 1260
cccgcgccgc ccccgactc ggagaccgac tcgcaggcgt cccgagagcg cagggtcaag 1320
aagaacttgg ccctgagtcg ggaaagtta gtcgtc 1356

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<210> SEQ ID NO 156

<211> LENGTH: 232

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 156

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Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1             5             10             15
Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
20            25            30
Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
35            40            45
Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
50            55            60
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65            70            75            80
Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
85            90            95
Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
100           105           110
Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
115           120           125
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
130           135           140
Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145           150           155           160
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
165           170           175
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
180           185           190
Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe

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195	200	205
Ser Cys Ser Val Met His	Glu Ala Leu His Asn His	Tyr Thr Gln Lys
210	215	220
Ser Leu Ser Leu Ser Pro Gly Lys		
225	230	

<210> SEQ ID NO 157
 <211> LENGTH: 217
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 157

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys	
1	15
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val	
20	30
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr	
35	45
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu	
50	60
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His	
65	80
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys	
85	95
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln	
100	110
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu	
115	125
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro	
130	140
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn	
145	160
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu	
165	175
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val	
180	190
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln	
195	205
Lys Ser Leu Ser Leu Ser Pro Gly Lys	
210	215

<210> SEQ ID NO 158
 <211> LENGTH: 217
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 158

Ala Pro Asn Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys	
1	15
Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro Ile Val Thr Cys Val	
20	30
Val Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln Ile Ser Trp Phe	
35	45

-continued

Val	Asn	Asn	Val	Glu	Val	His	Thr	Ala	Gln	Thr	Gln	Thr	His	Arg	Glu
50						55					60				
Asp	Tyr	Asn	Ser	Thr	Leu	Arg	Val	Val	Ser	Ala	Leu	Pro	Ile	Gln	His
65					70					75					80
Gln	Asp	Trp	Met	Ser	Gly	Lys	Glu	Phe	Lys	Cys	Lys	Val	Asn	Asn	Lys
			85						90					95	
Asp	Leu	Pro	Ala	Pro	Ile	Glu	Arg	Thr	Ile	Ser	Lys	Pro	Lys	Gly	Ser
			100					105					110		
Val	Arg	Ala	Pro	Gln	Val	Tyr	Val	Leu	Pro	Pro	Pro	Glu	Glu	Glu	Met
		115					120					125			
Thr	Lys	Lys	Gln	Val	Thr	Leu	Thr	Cys	Met	Val	Thr	Asp	Phe	Met	Pro
130						135					140				
Glu	Asp	Ile	Tyr	Val	Glu	Trp	Thr	Asn	Asn	Gly	Lys	Thr	Glu	Leu	Asn
145					150					155					160
Tyr	Lys	Asn	Thr	Glu	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Tyr	Phe	Met
			165					170						175	
Tyr	Ser	Lys	Leu	Arg	Val	Glu	Lys	Lys	Asn	Trp	Val	Glu	Arg	Asn	Ser
			180					185					190		
Tyr	Ser	Cys	Ser	Val	Val	His	Glu	Gly	Leu	His	Asn	His	His	Thr	Thr
		195					200				205				
Lys	Ser	Phe	Ser	Arg	Thr	Pro	Gly	Lys							
210						215									

<210> SEQ ID NO 159
 <211> LENGTH: 2
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 159

Gly Ser
1

<210> SEQ ID NO 160
 <211> LENGTH: 4
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 160

Gly Ser Gly Ser
1

<210> SEQ ID NO 161
 <211> LENGTH: 2
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 161

Ala Ser
1

<210> SEQ ID NO 162
 <211> LENGTH: 4
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

-continued

<400> SEQUENCE: 162

Gly Gly Gly Ser
1

<210> SEQ ID NO 163

<211> LENGTH: 5

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 163

Gly Gly Gly Gly Ser
1 5

<210> SEQ ID NO 164

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 164

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10

<210> SEQ ID NO 165

<211> LENGTH: 15

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 165

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> SEQ ID NO 166

<211> LENGTH: 20

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 166

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser
20

<210> SEQ ID NO 167

<211> LENGTH: 7

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 167

agaaaka

7

<210> SEQ ID NO 168

<211> LENGTH: 12

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

-continued

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 168

Ala Gly Ala Ala Ala Lys Gly Ala Ala Ala Lys Ala
 1 5 10

<210> SEQ ID NO 169

<211> LENGTH: 17

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 169

Ala Gly Ala Ala Ala Lys Gly Ala Ala Ala Lys Gly Ala Ala Ala Lys
 1 5 10 15

Ala

<210> SEQ ID NO 170

<211> LENGTH: 22

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 170

Ala Gly Ala Ala Ala Lys Gly Ala Ala Ala Lys Gly Ala Ala Ala Lys
 1 5 10 15

Gly Ala Ala Ala Lys Ala
 20

<210> SEQ ID NO 171

<211> LENGTH: 27

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 171

Ala Gly Ala Ala Ala Lys Gly Ala Ala Ala Lys Gly Ala Ala Ala Lys
 1 5 10 15

Gly Ala Ala Ala Lys Gly Ala Ala Ala Lys Ala
 20 25

<210> SEQ ID NO 172

<211> LENGTH: 450

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 172

Ala Asp Asn Met Gln Ala Ile Tyr Val Ala Leu Gly Glu Ala Val Glu
 1 5 10 15

Leu Pro Cys Pro Ser Pro Pro Thr Leu His Gly Asp Glu His Leu Ser
 20 25 30

Trp Phe Cys Ser Pro Ala Ala Gly Ser Phe Thr Thr Leu Val Ala Gln
 35 40 45

Val Gln Val Gly Arg Pro Ala Pro Asp Pro Gly Lys Pro Gly Arg Glu
 50 55 60

Ser Arg Leu Arg Leu Leu Gly Asn Tyr Ser Leu Trp Leu Glu Gly Ser
 65 70 75 80

Lys	Glu	Glu	Asp	Ala	Gly	Arg	Tyr	Trp	Cys	Ala	Val	Leu	Gly	Gln	His	
				85					90					95		
His	Asn	Tyr	Gln	Asn	Trp	Arg	Val	Tyr	Asp	Val	Leu	Val	Leu	Lys	Gly	
				100					105					110		
Ser	Gln	Leu	Ser	Ala	Arg	Ala	Ala	Asp	Gly	Ser	Pro	Cys	Asn	Val	Leu	
				115					120					125		
Leu	Cys	Ser	Val	Val	Pro	Ser	Arg	Arg	Met	Asp	Ser	Val	Thr	Trp	Gln	
				130					135					140		
Glu	Gly	Lys	Gly	Pro	Val	Arg	Gly	Arg	Val	Gln	Ser	Phe	Trp	Gly	Ser	
				145					150					155		
Glu	Ala	Ala	Leu	Leu	Leu	Val	Cys	Pro	Gly	Glu	Gly	Leu	Ser	Glu	Pro	
				165					170					175		
Arg	Ser	Arg	Arg	Pro	Arg	Ile	Ile	Arg	Cys	Leu	Met	Thr	His	Asn	Lys	
				180					185					190		
Gly	Val	Ser	Phe	Ser	Leu	Ala	Ala	Ser	Ile	Asp	Ala	Ser	Pro	Ala	Leu	
				195					200					205		
Cys	Ala	Pro	Ser	Thr	Gly	Trp	Asp	Met	Pro	Glu	Pro	Lys	Ser	Ser	Asp	
				210					215					220		
Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	
				225					230					235		
Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	
				245					250					255		
Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	
				260					265					270		
Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	
				275					280					285		
Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	
				290					295					300		
Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	
				305					310					315		
Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	
				325					330					335		
Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	
				340					345					350		
Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	
				355					360					365		
Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	
				370					375					380		
Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	
				385					390					395		
Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	
				405					410					415		
Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	
				420					425					430		
Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	
				435					440					445		
Gly	Lys															
				450												

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<210> SEQ ID NO 173
<211> LENGTH: 615
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide
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-continued

<400> SEQUENCE: 173

Val Val Ile Gly Glu Val His Glu Asn Val Thr Leu His Cys Gly Asn
 1 5 10 15
 Ile Ser Gly Leu Arg Gly Gln Val Thr Trp Tyr Arg Asn Asn Ser Glu
 20 25 30
 Pro Val Phe Leu Leu Ser Ser Asn Ser Ser Leu Arg Pro Ala Glu Pro
 35 40 45
 Arg Phe Ser Leu Val Asp Ala Thr Ser Leu His Ile Glu Ser Leu Ser
 50 55 60
 Leu Gly Asp Glu Gly Ile Tyr Thr Cys Gln Glu Ile Leu Asn Val Thr
 65 70 75 80
 Gln Trp Phe Gln Val Trp Leu Gln Val Ala Ser Gly Pro Tyr Gln Ile
 85 90 95
 Glu Val His Ile Val Ala Thr Gly Thr Leu Pro Asn Gly Thr Leu Tyr
 100 105 110
 Ala Ala Arg Gly Ser Gln Val Asp Phe Ser Cys Asn Ser Ser Ser Arg
 115 120 125
 Pro Pro Pro Val Val Glu Trp Trp Phe Gln Ala Leu Asn Ser Ser Ser
 130 135 140
 Glu Ser Phe Gly His Asn Leu Thr Val Asn Phe Phe Ser Leu Leu Leu
 145 150 155 160
 Ile Ser Pro Asn Leu Gln Gly Asn Tyr Thr Cys Leu Ala Leu Asn Gln
 165 170 175
 Leu Ser Lys Arg His Arg Lys Val Thr Thr Glu Leu Leu Val Tyr Tyr
 180 185 190
 Pro Pro Pro Ser Ala Pro Gln Cys Trp Ala Gln Met Ala Ser Gly Ser
 195 200 205
 Phe Met Leu Gln Leu Thr Cys Arg Trp Asp Gly Gly Tyr Pro Asp Pro
 210 215 220
 Asp Phe Leu Trp Ile Glu Glu Pro Gly Gly Val Ile Val Gly Lys Ser
 225 230 235 240
 Lys Leu Gly Val Glu Met Leu Ser Glu Ser Gln Leu Ser Asp Gly Lys
 245 250 255
 Lys Phe Lys Cys Val Thr Ser His Ile Val Gly Pro Glu Ser Gly Ala
 260 265 270
 Ser Cys Met Val Gln Ile Arg Gly Pro Ser Leu Leu Ser Glu Pro Met
 275 280 285
 Lys Thr Cys Phe Thr Gly Gly Asn Val Thr Leu Thr Cys Gln Val Ser
 290 295 300
 Gly Ala Tyr Pro Pro Ala Lys Ile Leu Trp Leu Arg Asn Leu Thr Gln
 305 310 315 320
 Pro Glu Val Ile Ile Gln Pro Ser Ser Arg His Leu Ile Thr Gln Asp
 325 330 335
 Gly Gln Asn Ser Thr Leu Thr Ile His Asn Cys Ser Gln Asp Leu Asp
 340 345 350
 Glu Gly Tyr Tyr Ile Cys Arg Ala Asp Ser Pro Val Gly Val Arg Glu
 355 360 365
 Met Glu Ile Trp Leu Ser Val Lys Glu Pro Leu Asn Ile Gly Gly Glu
 370 375 380
 Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
 385 390 395 400
 Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys

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405					410					415				
Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val
		420						425					430	
Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val
		435					440					445		Asp
Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln
	450					455					460			Tyr
Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln
	465					470					475			480
Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala
			485						490					495
Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro
		500						505					510	Arg
Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr
		515					520					525		Lys
Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser
	530					535					540			Asp
Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr
	545					550					555			560
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr
			565						570					575
Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe
		580						585					590	Ser
Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys
	595						600					605		Ser
Leu	Ser	Leu	Ser	Pro	Gly	Lys								
	610					615								

<210> SEQ ID NO 174

<211> LENGTH: 514

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 174

Val	Val	Ile	Gly	Glu	Val	His	Glu	Asn	Val	Thr	Leu	His	Cys	Gly	Asn
1			5						10					15	
Ile	Ser	Gly	Leu	Arg	Gly	Gln	Val	Thr	Trp	Tyr	Arg	Asn	Asn	Ser	Glu
		20						25					30		
Pro	Val	Phe	Leu	Leu	Ser	Ser	Asn	Ser	Ser	Leu	Arg	Pro	Ala	Glu	Pro
	35						40					45			
Arg	Phe	Ser	Leu	Val	Asp	Ala	Thr	Ser	Leu	His	Ile	Glu	Ser	Leu	Ser
	50					55					60				
Leu	Gly	Asp	Glu	Gly	Ile	Tyr	Thr	Cys	Gln	Glu	Ile	Leu	Asn	Val	Thr
	65				70					75				80	
Gln	Trp	Phe	Gln	Val	Trp	Leu	Gln	Val	Ala	Asn	Pro	Pro	Pro	Ser	Ala
		85						90						95	
Pro	Gln	Cys	Trp	Ala	Gln	Met	Ala	Ser	Gly	Ser	Phe	Met	Leu	Gln	Leu
		100						105					110		
Thr	Cys	Arg	Trp	Asp	Gly	Gly	Tyr	Pro	Asp	Pro	Asp	Phe	Leu	Trp	Ile
		115					120					125			
Glu	Glu	Pro	Gly	Gly	Val	Ile	Val	Gly	Lys	Ser	Lys	Leu	Gly	Val	Glu
	130					135					140				
Met	Leu	Ser	Glu	Ser	Gln	Leu	Ser	Asp	Gly	Lys	Lys	Phe	Lys	Cys	Val

-continued

145	150	155	160
Thr Ser His Ile Val Gly Pro Glu Ser Gly Ala Ser Cys Met Val Gln			
	165	170	175
Ile Arg Gly Pro Ser Leu Leu Ser Glu Pro Met Lys Thr Cys Phe Thr			
	180	185	190
Gly Gly Asn Val Thr Leu Thr Cys Gln Val Ser Gly Ala Tyr Pro Pro			
	195	200	205
Ala Lys Ile Leu Trp Leu Arg Asn Leu Thr Gln Pro Glu Val Ile Ile			
	210	215	220
Gln Pro Ser Ser Arg His Leu Ile Thr Gln Asp Gly Gln Asn Ser Thr			
	225	230	235
Leu Thr Ile His Asn Cys Ser Gln Asp Leu Asp Glu Gly Tyr Tyr Ile			
	245	250	255
Cys Arg Ala Asp Ser Pro Val Gly Val Arg Glu Met Glu Ile Trp Leu			
	260	265	270
Ser Val Lys Glu Pro Leu Asn Ile Gly Gly Glu Pro Lys Ser Ser Asp			
	275	280	285
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly			
	290	295	300
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile			
	305	310	315
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu			
	325	330	335
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His			
	340	345	350
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg			
	355	360	365
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys			
	370	375	380
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu			
	385	390	395
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr			
	405	410	415
Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu			
	420	425	430
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp			
	435	440	445
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val			
	450	455	460
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp			
	465	470	475
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His			
	485	490	495
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro			
	500	505	510
Gly Lys			

<210> SEQ ID NO 175

<211> LENGTH: 438

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 175

-continued

Glu	Leu	Glu	Pro	Gln	Ile	Asp	Gly	Gln	Thr	Trp	Ala	Glu	Arg	Ala	Leu	1	5	10	15
Arg	Glu	Asn	Glu	Arg	His	Ala	Phe	Thr	Cys	Arg	Val	Ala	Gly	Gly	Pro	20	25	30	
Gly	Thr	Pro	Arg	Leu	Ala	Trp	Tyr	Leu	Asp	Gly	Gln	Leu	Gln	Glu	Ala	35	40	45	
Ser	Thr	Ser	Arg	Leu	Leu	Ser	Val	Gly	Gly	Glu	Ala	Phe	Ser	Gly	Gly	50	55	60	
Thr	Ser	Thr	Phe	Thr	Val	Thr	Ala	His	Arg	Ala	Gln	His	Glu	Leu	Asn	65	70	75	80
Cys	Ser	Leu	Gln	Asp	Pro	Arg	Ser	Gly	Arg	Ser	Ala	Asn	Ala	Ser	Val	85	90	95	
Ile	Leu	Asn	Val	Gln	Phe	Lys	Pro	Glu	Ile	Ala	Gln	Val	Gly	Ala	Lys	100	105	110	
Tyr	Gln	Glu	Ala	Gln	Gly	Pro	Gly	Leu	Leu	Val	Val	Leu	Phe	Ala	Leu	115	120	125	
Val	Arg	Ala	Asn	Pro	Pro	Ala	Asn	Val	Thr	Trp	Ile	Asp	Gln	Asp	Gly	130	135	140	
Pro	Val	Thr	Val	Asn	Thr	Ser	Asp	Phe	Leu	Val	Leu	Asp	Ala	Gln	Asn	145	150	155	160
Tyr	Pro	Trp	Leu	Thr	Asn	His	Thr	Val	Gln	Leu	Gln	Leu	Arg	Ser	Leu	165	170	175	
Ala	His	Asn	Leu	Ser	Val	Val	Ala	Thr	Asn	Asp	Val	Gly	Val	Thr	Ser	180	185	190	
Ala	Ser	Leu	Pro	Ala	Pro	Gly	Leu	Leu	Ala	Thr	Arg	Val	Glu	Glu	Pro	195	200	205	
Lys	Ser	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	210	215	220	
Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	225	230	235	240
Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	245	250	255	
Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	260	265	270	
Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	275	280	285	
Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	290	295	300	
Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	305	310	315	320
Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	325	330	335	
Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	340	345	350	
Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	355	360	365	
Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	370	375	380	
Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	385	390	395	400
Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	405	410	415	

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Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
 420 425 430

Ser Leu Ser Pro Gly Lys
 435

<210> SEQ ID NO 176
 <211> LENGTH: 402
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 176

Ile Gln Val Thr Val Ser Asn Pro Tyr His Val Val Ile Leu Phe Gln
 1 5 10 15

Pro Val Thr Leu Pro Cys Thr Tyr Gln Met Thr Ser Thr Pro Thr Gln
 20 25 30

Pro Ile Val Ile Trp Lys Tyr Lys Ser Phe Cys Arg Asp Arg Ile Ala
 35 40 45

Asp Ala Phe Ser Pro Ala Ser Val Asp Asn Gln Leu Asn Ala Gln Leu
 50 55 60

Ala Ala Gly Asn Pro Gly Tyr Asn Pro Tyr Val Glu Cys Gln Asp Ser
 65 70 75 80

Val Arg Thr Val Arg Val Val Ala Thr Lys Gln Gly Asn Ala Val Thr
 85 90 95

Leu Gly Asp Tyr Tyr Gln Gly Arg Arg Ile Thr Ile Thr Gly Asn Ala
 100 105 110

Asp Leu Thr Phe Asp Gln Thr Ala Trp Gly Asp Ser Gly Val Tyr Tyr
 115 120 125

Cys Ser Val Val Ser Ala Gln Asp Leu Gln Gly Asn Asn Glu Ala Tyr
 130 135 140

Ala Glu Leu Ile Val Leu Gly Arg Thr Ser Gly Val Ala Glu Leu Leu
 145 150 155 160

Pro Gly Phe Gln Ala Gly Pro Ile Glu Asp Glu Pro Lys Ser Ser Asp
 165 170 175

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
 180 185 190

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
 195 200 205

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
 210 215 220

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
 225 230 235 240

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
 245 250 255

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
 260 265 270

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
 275 280 285

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
 290 295 300

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
 305 310 315 320

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
 325 330 335

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Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
 340 345 350

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
 355 360 365

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
 370 375 380

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
 385 390 395 400

Gly Lys

<210> SEQ ID NO 177
 <211> LENGTH: 383
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 177

Ile Gln Val Thr Val Ser Asn Pro Tyr His Val Val Ile Leu Phe Gln
 1 5 10 15

Pro Val Thr Leu Pro Cys Thr Tyr Gln Met Thr Ser Thr Pro Thr Gln
 20 25 30

Pro Ile Val Ile Trp Lys Tyr Lys Ser Phe Cys Arg Asp Arg Ile Ala
 35 40 45

Asp Ala Phe Ser Pro Ala Ser Val Asp Asn Gln Leu Asn Ala Gln Leu
 50 55 60

Ala Ala Gly Asn Pro Gly Tyr Asn Pro Tyr Val Glu Cys Gln Asp Ser
 65 70 75 80

Val Arg Thr Val Arg Val Val Ala Thr Lys Gln Gly Asn Ala Val Thr
 85 90 95

Leu Gly Asp Tyr Tyr Gln Gly Arg Arg Ile Thr Ile Thr Gly Asn Ala
 100 105 110

Asp Leu Thr Phe Asp Gln Thr Ala Trp Gly Asp Ser Gly Val Tyr Tyr
 115 120 125

Cys Ser Val Val Ser Ala Gln Asp Leu Gln Gly Asn Asn Glu Ala Tyr
 130 135 140

Ala Glu Leu Ile Val Leu Asp Glu Pro Lys Ser Ser Asp Lys Thr His
 145 150 155 160

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
 165 170 175

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
 180 185 190

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
 195 200 205

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
 210 215 220

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
 225 230 235 240

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
 245 250 255

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
 260 265 270

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
 275 280 285

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu

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290	295	300
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn		
305	310	315 320
Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser		
	325	330 335
Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg		
	340	345 350
Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu		
	355	360 365
His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys		
370	375	380

<210> SEQ ID NO 178
 <211> LENGTH: 724
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 178

Ile Gln Val Thr Val Ser Asn Pro Tyr His Val Val Ile Leu Phe Gln	
1	5 10 15
Pro Val Thr Leu Pro Cys Thr Tyr Gln Met Thr Ser Thr Pro Thr Gln	
	20 25 30
Pro Ile Val Ile Trp Lys Tyr Lys Ser Phe Cys Arg Asp Arg Ile Ala	
	35 40 45
Asp Ala Phe Ser Pro Ala Ser Val Asp Asn Gln Leu Asn Ala Gln Leu	
	50 55 60
Ala Ala Gly Asn Pro Gly Tyr Asn Pro Tyr Val Glu Cys Gln Asp Ser	
	65 70 75 80
Val Arg Thr Val Arg Val Val Ala Thr Lys Gln Gly Asn Ala Val Thr	
	85 90 95
Leu Gly Asp Tyr Tyr Gln Gly Arg Arg Ile Thr Ile Thr Gly Asn Ala	
	100 105 110
Asp Leu Thr Phe Asp Gln Thr Ala Trp Gly Asp Ser Gly Val Tyr Tyr	
	115 120 125
Cys Ser Val Val Ser Ala Gln Asp Leu Gln Gly Asn Asn Glu Ala Tyr	
	130 135 140
Ala Glu Leu Ile Val Leu Val Tyr Ala Ala Gly Lys Ala Ala Thr Ser	
	145 150 155 160
Gly Val Pro Ser Ile Tyr Ala Pro Ser Thr Tyr Ala His Leu Ser Pro	
	165 170 175
Ala Lys Thr Pro Pro Pro Pro Ala Met Ile Pro Met Gly Pro Ala Tyr	
	180 185 190
Asn Gly Tyr Pro Gly Gly Tyr Pro Gly Asp Val Asp Arg Ser Ser Ser	
	195 200 205
Ala Gly Gly Gln Gly Ser Tyr Val Pro Leu Leu Arg Asp Thr Asp Ser	
	210 215 220
Ser Val Ala Ser Glu Val Arg Ser Gly Tyr Arg Ile Gln Ala Ser Gln	
	225 230 235 240
Gln Asp Asp Ser Met Arg Val Leu Tyr Tyr Met Glu Lys Glu Leu Ala	
	245 250 255
Asn Phe Asp Pro Ser Arg Pro Gly Pro Pro Ser Gly Arg Val Glu Arg	
	260 265 270
Ala Met Ser Glu Val Thr Ser Leu His Glu Asp Asp Trp Arg Ser Arg	

275				280				285							
Pro 290	Ser	Arg	Gly	Pro	Ala	Leu 295	Thr	Pro	Ile	Arg	Asp 300	Glu	Glu	Trp	Gly
Gly 305	His	Ser	Pro	Arg	Ser 310	Pro	Arg	Gly	Trp	Asp 315	Gln	Glu	Pro	Ala	Arg 320
Glu	Gln	Ala	Gly 325	Gly	Trp	Arg	Ala 330	Arg	Arg	Pro	Arg	Ala	Arg 335	Ser	
Val	Asp	Ala 340	Leu	Asp	Asp	Leu	Thr 345	Pro	Ser	Thr	Ala 350	Glu	Ser	Gly	
Ser	Arg 355	Ser	Pro	Thr	Ser	Asn 360	Gly	Arg	Ser	Arg 365	Tyr	Met	Pro		
Pro 370	Arg	Ser	Arg	Ser	Arg 375	Asp	Asp	Leu	Tyr	Asp 380	Gln	Asp	Asp	Ser	Arg
Asp 385	Phe	Pro 385	Arg	Ser	Arg 390	Asp	Pro	His	Tyr	Asp 395	Asp	Phe	Arg	Ser	Arg 400
Glu	Arg	Pro	Pro 405	Ala	Asp	Pro	Arg	Ser	His 410	His	His	Arg	Thr	Arg 415	Asp
Pro	Arg	Asp	Asn 420	Gly	Ser	Arg	Ser	Gly 425	Asp	Leu	Pro	Tyr	Asp 430	Gly	Arg
Leu	Leu 435	Glu	Glu	Ala	Val	Arg	Lys 440	Lys	Gly	Ser	Glu	Glu 445	Arg	Arg	Arg
Pro 450	His	Lys	Glu	Glu	Glu 455	Glu	Ala	Tyr	Tyr	Pro 460	Pro	Ala	Pro	Pro	
Pro 465	Tyr	Ser	Glu	Thr	Asp 470	Ser	Gln	Ala	Ser	Arg 475	Glu	Arg	Arg	Leu	Lys 480
Lys	Asn	Leu	Ala 485	Leu	Ser	Arg	Glu	Ser	Leu 490	Val	Val	Glu	Pro	Lys 495	Ser
Ser	Asp	Lys 500	Thr	His	Thr	Cys	Pro	Pro 505	Cys	Pro	Ala	Pro	Glu 510	Leu	Leu
Gly	Gly 515	Pro	Ser	Val	Phe	Leu	Phe 520	Pro	Pro	Lys	Pro	Lys 525	Asp	Thr	Leu
Met 530	Ile	Ser	Arg	Thr	Pro	Glu 535	Val	Thr	Cys	Val	Val 540	Val	Asp	Val	Ser
His 545	Glu	Asp	Pro	Glu	Val 550	Lys	Phe	Asn	Trp	Tyr	Val 555	Asp	Gly	Val	Glu 560
Val	His	Asn	Ala 565	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr
Tyr	Arg	Val 580	Val	Ser	Val	Leu	Thr	Val 585	Leu	His	Gln	Asp	Trp 590	Leu	Asn
Gly	Lys 595	Glu	Tyr	Lys	Cys	Lys	Val 600	Ser	Asn	Lys	Ala	Leu 605	Pro	Ala	Pro
Ile 610	Glu	Lys	Thr	Ile	Ser	Lys 615	Ala	Lys	Gly	Gln	Pro 620	Arg	Glu	Pro	Gln
Val 625	Tyr	Thr	Leu	Pro	Pro 630	Ser	Arg	Asp	Glu	Leu	Thr 635	Lys	Asn	Gln	Val 640
Ser	Leu	Thr	Cys 645	Leu	Val	Lys	Gly	Phe	Tyr	Pro 650	Ser	Asp	Ile	Ala	Val 655
Glu	Trp	Glu 660	Ser	Asn	Gly	Gln	Pro	Glu 665	Asn	Asn	Tyr	Lys	Thr 670	Thr	Pro
Pro	Val 675	Leu	Asp	Ser	Asp	Gly	Ser	Phe 680	Phe	Leu	Tyr	Ser 685	Lys	Leu	Thr
Val 690	Asp	Lys	Ser	Arg	Trp 695	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	

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Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
705 710 715 720

Ser Pro Gly Lys

<210> SEQ ID NO 179
<211> LENGTH: 723
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 179

Ile Gln Val Thr Val Ser Asn Pro Tyr His Val Val Ile Leu Phe Gln
1 5 10 15
Pro Val Thr Leu Pro Cys Thr Tyr Gln Met Thr Ser Thr Pro Thr Gln
20 25 30
Pro Ile Val Ile Trp Lys Tyr Lys Ser Phe Cys Arg Asp Arg Ile Ala
35 40 45
Asp Ala Phe Ser Pro Ala Ser Val Asp Asn Gln Leu Asn Ala Gln Leu
50 55 60
Ala Ala Gly Asn Pro Gly Tyr Asn Pro Tyr Val Glu Cys Gln Asp Ser
65 70 75 80
Val Arg Thr Val Arg Val Val Ala Thr Lys Gln Gly Asn Ala Val Thr
85 90 95
Leu Gly Asp Tyr Tyr Gln Gly Arg Arg Ile Thr Ile Thr Gly Asn Ala
100 105 110
Asp Leu Thr Phe Asp Gln Thr Ala Trp Gly Asp Ser Gly Val Tyr Tyr
115 120 125
Cys Ser Val Val Ser Ala Gln Asp Leu Gln Gly Asn Asn Glu Ala Tyr
130 135 140
Ala Glu Leu Ile Val Leu Val Tyr Ala Ala Gly Lys Ala Ala Thr Ser
145 150 155 160
Gly Val Pro Ser Ile Tyr Ala Pro Ser Thr Tyr Ala His Leu Ser Pro
165 170 175
Ala Lys Thr Pro Pro Pro Pro Ala Met Ile Pro Met Gly Pro Ala Tyr
180 185 190
Asn Gly Tyr Pro Gly Gly Tyr Pro Gly Asp Val Asp Arg Ser Ser Ser
195 200 205
Ala Gly Gly Gln Gly Ser Tyr Val Pro Leu Leu Arg Asp Thr Asp Ser
210 215 220
Ser Val Ala Ser Val Arg Ser Gly Tyr Arg Ile Gln Ala Ser Gln Gln
225 230 235 240
Asp Asp Ser Met Arg Val Leu Tyr Tyr Met Glu Lys Glu Leu Ala Asn
245 250 255
Phe Asp Pro Ser Arg Pro Gly Pro Pro Ser Gly Arg Val Glu Arg Ala
260 265 270
Met Ser Glu Val Thr Ser Leu His Glu Asp Asp Trp Arg Ser Arg Pro
275 280 285
Ser Arg Gly Pro Ala Leu Thr Pro Ile Arg Asp Glu Glu Trp Gly Gly
290 295 300
His Ser Pro Arg Ser Pro Arg Gly Trp Asp Gln Glu Pro Ala Arg Glu
305 310 315 320
Gln Ala Gly Gly Gly Trp Arg Ala Arg Arg Pro Arg Ala Arg Ser Val
325 330 335

[illegible]

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<210> SEQ ID NO 180
<211> LENGTH: 684
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
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-continued

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polypeptide

<400> SEQUENCE: 180

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Ile Gln Val Thr Val Ser Asn Pro Tyr His Val Val Ile Leu Phe Gln
1          5          10          15

Pro Val Thr Leu Pro Cys Thr Tyr Gln Met Thr Ser Thr Pro Thr Gln
20          25          30

Pro Ile Val Ile Trp Lys Tyr Lys Ser Phe Cys Arg Asp Arg Ile Ala
35          40          45

Asp Ala Phe Ser Pro Ala Ser Val Asp Asn Gln Leu Asn Ala Gln Leu
50          55          60

Ala Ala Gly Asn Pro Gly Tyr Asn Pro Tyr Val Glu Cys Gln Asp Ser
65          70          75          80

Val Arg Thr Val Arg Val Val Ala Thr Lys Gln Gly Asn Ala Val Thr
85          90          95

Leu Gly Asp Tyr Tyr Gln Gly Arg Arg Ile Thr Ile Thr Gly Met Tyr
100         105         110

Ala Ala Gly Lys Ala Ala Thr Ser Gly Val Pro Ser Ile Tyr Ala Pro
115         120         125

Ser Thr Tyr Ala His Leu Ser Pro Ala Lys Thr Pro Pro Pro Pro Ala
130         135         140

Met Ile Pro Met Gly Pro Ala Tyr Asn Gly Tyr Pro Gly Gly Tyr Pro
145         150         155         160

Gly Asp Val Asp Arg Ser Ser Ser Ala Gly Gly Gln Gly Ser Tyr Val
165         170         175

Pro Leu Leu Arg Asp Thr Asp Ser Ser Val Ala Ser Glu Val Arg Ser
180         185         190

Gly Tyr Arg Ile Gln Ala Ser Gln Gln Asp Asp Ser Met Arg Val Leu
195         200         205

Tyr Tyr Met Glu Lys Glu Leu Ala Asn Phe Asp Pro Ser Arg Pro Gly
210         215         220

Pro Pro Ser Gly Arg Val Glu Arg Ala Met Ser Glu Val Thr Ser Leu
225         230         235         240

His Glu Asp Asp Trp Arg Ser Arg Pro Ser Arg Gly Pro Ala Leu Thr
245         250         255

Pro Ile Arg Asp Glu Glu Trp Gly Gly His Ser Pro Arg Ser Pro Arg
260         265         270

Gly Trp Asp Gln Glu Pro Ala Arg Glu Gln Ala Gly Gly Gly Trp Arg
275         280         285

Ala Arg Arg Pro Arg Ala Arg Ser Val Asp Ala Leu Asp Asp Leu Thr
290         295         300

Pro Pro Ser Thr Ala Glu Ser Gly Ser Arg Ser Pro Thr Ser Asn Gly
305         310         315         320

Gly Arg Ser Arg Ala Tyr Met Pro Pro Arg Ser Arg Ser Arg Asp Asp
325         330         335

Leu Tyr Asp Gln Asp Asp Ser Arg Asp Phe Pro Arg Ser Arg Asp Pro
340         345         350

His Tyr Asp Asp Phe Arg Ser Arg Glu Arg Pro Pro Ala Asp Pro Arg
355         360         365

Ser His His His Arg Thr Arg Asp Pro Arg Asp Asn Gly Ser Arg Ser
370         375         380

Gly Asp Leu Pro Tyr Asp Gly Arg Leu Leu Glu Glu Ala Val Arg Lys
385         390         395         400

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Val	Arg	Thr	Val	Arg	Val	Val	Ala	Thr	Lys	Gln	Gly	Asn	Ala	Val	Thr
Leu	Gly	Asp	Tyr	Tyr	Gln	Gly	Arg	Arg	Ile	Thr	Ile	Thr	Gly	Asn	Ala
Asp	Leu	Thr	Phe	Asp	Gln	Thr	Ala	Trp	Gly	Asp	Ser	Gly	Val	Tyr	Tyr
Cys	Ser	Val	Val	Ser	Ala	Gln	Asp	Leu	Gln	Gly	Asn	Asn	Glu	Ala	Tyr
Ala	Glu	Leu	Ile	Val	Leu	Gly	Arg	Thr	Ser	Gly	Val	Ala	Glu	Leu	Leu
Pro	Gly	Phe	Gln	Ala	Gly	Pro	Ile	Glu	Val	Tyr	Ala	Ala	Gly	Lys	Ala
Ala	Thr	Ser	Gly	Val	Pro	Ser	Ile	Tyr	Ala	Pro	Ser	Thr	Tyr	Ala	His
Leu	Ser	Pro	Ala	Lys	Thr	Pro	Pro	Pro	Pro	Ala	Met	Ile	Pro	Met	Gly
Pro	Ala	Tyr	Asn	Gly	Tyr	Pro	Gly	Gly	Tyr	Pro	Gly	Asp	Val	Asp	Arg
Ser	Ser	Ser	Ala	Gly	Gly	Gln	Gly	Ser	Tyr	Val	Pro	Leu	Leu	Arg	Asp
Thr	Asp	Ser	Ser	Val	Ala	Ser	Glu	Val	Arg	Ser	Gly	Tyr	Arg	Ile	Gln
Ala	Ser	Gln	Gln	Asp	Asp	Ser	Met	Arg	Val	Leu	Tyr	Tyr	Met	Glu	Lys
Glu	Leu	Ala	Asn	Phe	Asp	Pro	Ser	Arg	Pro	Gly	Pro	Pro	Ser	Gly	Arg
Val	Glu	Arg	Ala	Met	Ser	Glu	Val	Thr	Ser	Leu	His	Glu	Asp	Asp	Trp
Arg	Ser	Arg	Pro	Ser	Arg	Gly	Pro	Ala	Leu	Thr	Pro	Ile	Arg	Asp	Glu
Glu	Trp	Gly	Gly	His	Ser	Pro	Arg	Ser	Pro	Arg	Gly	Trp	Asp	Gln	Glu
Pro	Ala	Arg	Glu	Gln	Ala	Gly	Gly	Gly	Trp	Arg	Ala	Arg	Arg	Pro	Arg
Ala	Arg	Ser	Val	Asp	Ala	Leu	Asp	Asp	Leu	Thr	Pro	Pro	Ser	Thr	Ala
Glu	Ser	Gly	Ser	Arg	Ser	Pro	Thr	Ser	Asn	Gly	Gly	Arg	Ser	Arg	Ala
Tyr	Met	Pro	Pro	Arg	Ser	Arg	Ser	Arg	Asp	Asp	Leu	Tyr	Asp	Gln	Asp
Asp	Ser	Arg	Asp	Phe	Pro	Arg	Ser	Arg	Asp	Pro	His	Tyr	Asp	Asp	Phe
Arg	Ser	Arg	Glu	Arg	Pro	Pro	Ala	Asp	Pro	Arg	Ser	His	His	His	Arg
Thr	Arg	Asp	Pro	Arg	Asp	Asn	Gly	Ser	Arg	Ser	Gly	Asp	Leu	Pro	Tyr
Asp	Gly	Arg	Leu	Leu	Glu	Glu	Ala	Val	Arg	Lys	Lys	Gly	Ser	Glu	Glu
Arg	Arg	Arg	Pro	His	Lys	Glu	Glu	Glu	Glu	Glu	Ala	Tyr	Tyr	Pro	Pro
Ala	Pro	Pro	Pro	Tyr	Ser	Glu	Thr	Asp	Ser	Gln	Ala	Ser	Arg	Glu	Arg

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Arg Leu Lys Lys Asn Leu Ala Leu Ser Arg Glu Ser Leu Val Val Glu
 500 505 510
 Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
 515 520 525
 Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
 530 535 540
 Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
 545 550 555 560
 Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
 565 570 575
 Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
 580 585 590
 Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
 595 600 605
 Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
 610 615 620
 Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
 625 630 635 640
 Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
 645 650 655
 Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
 660 665 670
 Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
 675 680 685
 Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
 690 695 700
 Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
 705 710 715 720
 Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
 725 730 735
 Leu Ser Leu Ser Pro Gly Lys
 740

<210> SEQ ID NO 182

<211> LENGTH: 702

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 182

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atggcagtct tattcctcct cctgttecta tgtggaactc cccaggctgc agacaacatg      60
caggccatct atgtggcctt gggggaggca gtagagctgc catgtccctc accacctact      120
ctacatgggg acgaacacct gtcatgggtc tgcagccctg cagcaggctc cttcaccacc      180
ctggtagccc aagtccaagt gggcaggcca gcccagacc ctggaaaacc aggaagggaa      240
tccaggctca gactgctggg gaactattct ttgtggttgg agggatccaa agaggaagat      300
gccgggcggt actggtgcgc tgtgctaggt cagcaccaca actaccagaa ctggagggtg      360
tacgacgtct tgggtgctca aggatcccag ttatctgcaa gggctgcaga tggatcccc      420
tgcaatgtcc tcctgtgctc tgtggtcccc agcagacgca tggactctgt gacctggcag      480
gaagggaagg gtcccgtag gggccgtgtt cagtccttct ggggcagtga ggctgcctg      540
ctcttggtgt gtctgggga ggggctttct gagcccagga gccgaagacc aagaatcatc      600
cgctgcctca tgactcacia caaaggggtc agctttagcc tggcagcctc catcgatgct      660

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tctcctgccc tctgtgcccc ttccacgggc tgggacatgc ct 702

<210> SEQ ID NO 183
 <211> LENGTH: 1239
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 183

atggccgcag gcggcagtcg gcccgagccc cgcgtcctcg tctgcctcgg ggcgctcctg	60
gccggctggg tcgccgtagg attggaggct gttgtcattg gagaagttca tgagaatgtt	120
actctgcact gtggcaacat ctccgggactg agggggccagg tgacctggta ccggaacaac	180
tcggagcctg tcttccttct ctcgcccaac tctagcctcc ggccagctga gcctcgcttc	240
tctctagtgg atgccacctc cctgcacatt gaatcgctga gcctgggaga tgagggaatc	300
tacacctgcc aggagatcct gaatgtgact cagtgggtcc aagtgtggct gcagggtggc	360
agcggccccct atcagattga ggtccacatc gtggccacgg gcacactccc caacggcacc	420
ctctatgcag ccaggggctc ccagggtggac ttcagctgca acagcagctc caggccacca	480
cccgtggttg aatggtggtt ccaggccctg aattccagca gcgagtcctt tggccacaac	540
ctgacagtca actttttctc actgttactg atatcgccaa acctccaagg gaactacacc	600
tgtttagcct tgaatcagct cagcaagaga catcgaaagg tgaccaccga gctcctggtc	660
tactatcccc ctccatcagc tccccagtcg tgggcacaga tggcatcagg atcgttcatg	720
ttgcagctta cctgtcgtcg ggatggggga taccctgacc ctgacttctc gtggatagaa	780
gagccaggag gtgtaatcgt ggggaagtca aagctggggg tggaaatgct gagcgagtcc	840
cagctgtcgg atggcaagaa gttcaagtgt gttacaagcc acatagttag gccagagtgc	900
ggcgccagct gcattggtga gatcaggggt cctcccttc tctctgagcc catgaagact	960
tgcttctactg ggggcaatgt gacgcttaca tgccagggtg ctggggccta cccccctgcc	1020
aagatcctgt ggctgaggaa ccttaccag cccgagggtg tcatccagcc tagcagccgc	1080
catctcatta cccaggatgg ccagaactcc accctcacta tccacaactg ctcccaggac	1140
ctggatgagg gctactacat ctgccagct gacagccctg taggggtgag ggagatggaa	1200
atctggctga gttgaaaaga acctttaaat atcggggggg	1239

<210> SEQ ID NO 184
 <211> LENGTH: 936
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 184

atggccgcag gcggcagtcg gcccgagccc cgcgtcctcg tctgcctcgg ggcgctcctg	60
gccggctggg tcgccgtagg attggaggct gttgtcattg gagaagttca tgagaatgtt	120
actctgcact gtggcaacat ctccgggactg agggggccagg tgacctggta ccggaacaac	180
tcggagcctg tcttccttct ctcgcccaac tctagcctcc ggccagctga gcctcgcttc	240
tctctagtgg atgccacctc cctgcacatt gaatcgctga gcctgggaga tgagggaatc	300
tacacctgcc aggagatcct gaatgtgact cagtgggtcc aagtgtggct gcagggtggc	360
aatccccctc catcagctcc ccagtgtggt gcacagatgg catcaggatc gttcatgttg	420

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cagcttacct gtcgctggga tgggggatac cctgacctg acttctctgtg gatagaagag	480
ccaggagggtg taatcgtggg gaagtcaaag ctgggggtgg aaatgctgag cgagtcccag	540
ctgtcggatg gcaagaagtt caagtgtgtt acaagccaca tagttgggcc agagtcgggc	600
gccagctgca tgggtcagat caggggtccc tcccttctct ctgagcccat gaagacttgc	660
ttcactgggg gcaatgtgac gcttacatgc caggtgtctg gggcctaccc ccctgccaa	720
atcctgtggc tgaggaacct taccagccc gaggtgatca tccagcctag cagccgccat	780
ctcattaccc aggatggcca gaactccacc ctactatcc acaactgctc ccaggacctg	840
gatgagggt actacatctg ccgagctgac agccctgtag gggtagaggga gatggaaatc	900
tggtctgagtg tgaaagaacc tttaaataac gggggg	936

<210> SEQ ID NO 185
 <211> LENGTH: 690
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 185

atggcgctgc ctccaggccc agccgccctc cggcacacac tgetgtctct gccagccctt	60
ctgagctcag gttgggggga gttggagcca caaatagatg gtcagacctg ggctgagcgg	120
gcacttcggg agaatgaacg ccacgccttc acctgccggg tggcaggggg gcctggcacc	180
cccagattgg cctggtatct ggatggacag ctgcaggagg ccagcacctc aagactgctg	240
agcgtgggag gggaggcctt ctctggaggc accagcacct tcaactgtac tgcccatcgg	300
gcccagcatg agctcaactg ctctctgcag gaccccagaa gtggccgac agccaacgcc	360
tctgtcatcc ttaatgtgca attcaagcca gagattgccc aagtgcggcg caagtaccag	420
gaagctcagg gccaggcct cctggttgtc ctgtttgccc tgggtgcgtgc caaccgccg	480
gccaatgtca cctggatcga ccaggatggg ccagtgaactg tcaacacctc tgacttctctg	540
gtgctggatg cgcagaacta cccctggctc accaaccaca cgggtgcagct gcagctccgc	600
agcctggcac acaacctctc ggtggtggcc accaatgacg tgggtgtcac cagtgcgtcg	660
cttcagccc cagggttctt ggtacccgg	690

<210> SEQ ID NO 186
 <211> LENGTH: 633
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 186

atggcgctgt tggccggcgg gctctccaga gggctgggct cccaccggc cgcgcaggc	60
cgggacgcgg tcgtctctgt gtggcttctg cttagcacct ggtgcacagc tctgcccagg	120
gccatccagg tgaccgtgtc caaccctac cacgtggtga tctctctcca gcctgtgacc	180
ctgccctgta cctaccagat gacctcgacc cccacgcaac ccatcgctcat ctggaagtac	240
aagtctttct gccgggaccg catcgccgat gccttctccc cggccagcgt cgacaaccag	300
ctcaatgccc agctggcagc cgggaaccca ggctacaacc cctacgtcga gtgccaggac	360
agcgtgcgca ccgtcagggt cgtggccacc aagcagggca acgtgtgac cctgggagat	420
tactaccagg gccggaggat taccatcacc ggaaatgctg acctgacctt tgaccagacg	480
gcgtgggggg acagtgggtg gtattactgc tccgtggtct cagcccagga cctccagggg	540

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aacaatgagg cctacgcaga gctcatcgtc cttgggagga cctcaggggt ggctgagctc 600
ttacctgggtt ttcaggcggg gcccatagaa gac 633
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<210> SEQ ID NO 187
<211> LENGTH: 576
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide
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<400> SEQUENCE: 187
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atggcgctgt tggccggcgg gctctccaga gggctgggct cccacccggc cgccgcaggc 60
cgggacgcgg tcgtcttcgt gtggcttctg cttagcacct ggtgcacagc tcctgccagg 120
gccatccagg tgaccgtgtc caaccctac cagtggtga tccttttcca gcctgtgacc 180
ctgccctgta cctaccagat gacctcgacc cccacgcaac ccatcgtcac ctggaagtac 240
aagtctttct gccgggaccg catcgccgat gccttctccc cgggcagcgt cgacaaccag 300
ctcaatgccc agctggcagc cggaaccca ggctacaacc cctacgtcga gtgccaggac 360
agcgtgcgca ccgtcagggc cgtggccacc aagcagggca acgctgtgac cctgggagat 420
tactaccagg gccggaggat taccatcacc ggaaatgctg acctgacctt tgaccagacg 480
gcgtgggggg acagtgtgtg gtattactgc tccgtgtgtc cagcccagga cctccagggg 540
aacaatgagg cctacgcaga gctcatcgtc cttgac 576
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<210> SEQ ID NO 188
<211> LENGTH: 1533
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide
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<400> SEQUENCE: 188
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atccaggatga ccgtgtccaa cccctaccac gtggtgatcc tcttcagcc tgtgacctg 60
ccctgtacct accagatgac ctgcaccccc acgcaaccca tcgtcatctg gaagtacaag 120
tctttctgcc gggaccgcat cgccgatgcc ttctccccgg ccagcgtcga caaccagctc 180
aatgcccagc tggcagccgg gaaccaggc tacaaccctc acgtcgagtg ccaggacagc 240
gtgcgcaccg tcagggtcgt ggcaccaag cagggcaacg ctgtgacctt gggagattac 300
taccagggcc ggaggattac catcacggga aatgtgacc tgacctttga ccagcggcg 360
tggggggaca gtggtgtgta ttactgctc gtggtctcag ccaggacct ccaggggaac 420
aatgaggcct acgcagagct catcgctctt gggaggacct caggggtggc tgagctctta 480
cctggttttc aggcggggcc catagaagtg tatgcgcgg gcaaagcagc cacctcaggt 540
gttcccagca tttatgcccc cagcacctat gccacctgt ctccgccaa gaccccaccc 600
ccaccagcta tgattcccat gggccctgcc tacaacgggt acctggagg atacctgga 660
gacgttgaca ggagtagctc agctggtggc caaggctcct atgtacctt gcttcgggac 720
acggacagca gtgtggcctc tgaagtccgc agtggctaca ggattcaggc cagccagcag 780
gacgactcca tgcgggtcct gtactacatg gagaaggagc tggccaactt cgaccttct 840
cgacctggcc cccccagtgg ccgtgtggag cgggccaatga gtgaagtcac ctccctccac 900
gaggacgact ggcgatctcg gccttcccgg ggccctgccc tcaccccgat ccgggatgag 960
gagtgggggtg gccactcccc ccggagtccc aggggatggg accaggagcc cgccagggag 1020
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caggcaggcg ggggctggcg ggccaggcgg ccccgggccc gctccgtgga cgccctggac	1080
gacctcaccg cgccgagcac cgccgagtca gggagcaggt ctcccacgag taatggtggg	1140
agaagccggg cctacatgcc ccgcgggagc cgcagccggg acgacctcta tgaccaagac	1200
gactcgaggg acttcccacg ctcccgggac ccccaactacg acgacttcag gtctcgggag	1260
cgccctcctg ccgaccccag gtcccaccac caccgtaccc gggaccctcg ggacaacggc	1320
tccagggtccg gggacctccc ctatgatggg cggtactagg aggaggctgt gaggaagaag	1380
gggtcggagg agaggaggag accccacaag gaggaggagg aagaggccta ctaccgccc	1440
gcgcgcgccc cgtactcgga gaccgactcg caggcgctccc gagagcgag gctcaagaag	1500
aacttgcccc tgagtcggga aagtttagtc gtc	1533

<210> SEQ ID NO 189

<211> LENGTH: 1398

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 189

atggcagttt tattcctcct cctgttcccta tgtggaactc cccaggctgc agacaacatg	60
caggccatct atgtggcctt gggggaggga gtagagctgc catgtccctc accacctact	120
ctacatgggg acgaacacct gtcagtgttc tgcagccctg cagcaggttc cttcaccacc	180
ctggtagccc aagtccaagt gggcaggcca gcccagacc ctggaaaacc aggaaggga	240
tccaggctca gactgctggg gaactattct ttgtggttgg agggatccaa agaggaagat	300
gccggggcgt actggtgcgc tgtgctaggt cagcaccaca actaccagaa ctggagggtg	360
tacgacgtct tgggtctcaa aggatcccag ttatctgcaa gggctgcaga tggatcccc	420
tgcaatgtcc tcctgtgtc tgtggtcccc agcagacgca tggactctgt gacctggcag	480
gaagggaagg gtccctgtgag gggcgctgtt cagtcctctc ggggcagtga ggctgccctg	540
ctcttggtgt gtctgggga ggggctttct gagcccagga gccgaagacc aagaatcctc	600
cgctgcctca tgactcaca caaaggggtc agctttagcc tggcagcctc catcgatgct	660
tctctgccc tctgtgccc ttccacgggc tgggacatgc ctgagcccaa atcttctgac	720
aaaactcaca catgccacc gtgcccagca cctgaactcc tgggggggacc gtcagtcttc	780
ctcttcccc caaaacccaa ggacacctc atgatctccc ggacctctga ggtaacatgc	840
gtggtggtgg acgtgagcca cgaagacctt gagggtcaagt tcaactggta cgtggacggc	900
gtggagggtc ataatgcaa gacaaagccg cgggaggagc agtacaacag cacgtaccgt	960
gtggtcagcg tcctcacctg cctgcaccag gactggctga atggcaagga gtacaagtgc	1020
aaggctctca acaaaagcct cccagcccc atcgagaaaa ccatctccaa agccaaaggg	1080
cagccccgag aaccacaggt gtacacctc ccccatccc gggatgagct gaccaagaac	1140
caggtcagcc tgacctgctt ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg	1200
gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgctgt ggactccgac	1260
ggctccttct tcctctacag caagctcacc gtggacaaga gcagggtggc gcaggggaac	1320
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc	1380
tcctgtctc cgggtaaa	1398

<210> SEQ ID NO 190

<211> LENGTH: 1935

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<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 190

atggccgcag gcggcagtgc gcccgagccc cgcgtcctcg tctgcctcgg ggcgctcctg    60
gccggctggg tcgccgtagg attggaggct gttgtcattg gagaagttca tgagaatgtt    120
actctgcact gtggcaacat ctccgggactg agggggccagg tgacctggtg ccggaacaac    180
tcggagcctg tcttccttct ctcgcccaac tctagcctcc ggccagctga gcctcgcttc    240
tctctagtgg atgccacctc cctgcacatt gaatcgctga gcctgggaga tgagggaatc    300
tacacctgcc aggagatcct gaatgtgact cagtgggtcc aagtgtggct gcagggtggc    360
agcggccctc atcagattga ggtccacatc gtggccaccg gcacactccc caacggcacc    420
ctctatgcag ccaggggctc ccagggtggac ttcagctgca acagcagctc caggccacca    480
cccgtggttg aatggtggtt ccaggccctg aattccagca gcgagtcctt tggccacaac    540
ctgacagtca actttttctc actgttactg atatcgccaa acctccaagg gaactacacc    600
tgtttagcct tgaatcagct cagcaagaga catcgaaagg tgaccaccga gctcctggtc    660
tactatcccc ctccatcagc tccccagtc tgggcacaga tggcatcagg atcgttcatg    720
ttgcagctta cctgtcgtcg ggatggggga taccctgacc ctgacttctc gtggatagaa    780
gagccaggag gtgtaatcgt ggggaagtca aagctggggg tggaaatgct gagcgagtcc    840
cagctgtcgg atggcaagaa gttcaagtgt gttacaagcc acatagtggg gccagagtgc    900
ggcgccagct gcattggtga gatcaggggt cctcccttc tctctgagcc catgaagact    960
tgcttctact ggggcaatgt gacgcttaca tgccagggtg ctggggccta cccccctgcc   1020
aagatcctgt ggctgaggaa ccttaccag cccgagggtg tcatccagcc tagcagccgc   1080
catctcatta cccaggatgg ccagaactcc accctcacta tccacaactg ctcccaggac   1140
ctggatgagg gctactacat ctgccgagct gacagccctg taggggtgag ggagatggaa   1200
atctggctga gtgtgaaaga acctttaaat atcggggggg agcccaaacc ttctgacaaa   1260
actcacacat gccccacgtg cccagcacct gaactcctgg ggggaccgtc agtcttcttc   1320
ttccccccaa aacccaagga caccctcatg atctcccga cccctgaggt cacatgcgtg   1380
gtggtggacg tgagccacga agaccctgag gtcaagtcca actgggtacgt ggacggcgtg   1440
gagggtgcata atgccaagac aaagccgcgg gaggagcagt acaacagcac gtaccgtgtg   1500
gtcagcgtcc tcaccgtcct gcaccaggac tggctgaatg gcaaggagta caagtgcaag   1560
gtctccaaca aagccctccc agcccccatc gagaaaacca tctccaaagc caaagggcag   1620
ccccgagaac cacagggtga caccctgccc ccatcccggy atgagctgac caagaaccag   1680
gtcagcctga cctgcctggt caaaggcttc tatcccagcg acatgcctgt ggagtgggag   1740
agcaatgggc agccggagaa caactacaag accacgcctc ccgtgtctga ctccgacggc   1800
tccttcttcc tctacagcaa gctcaccgtg gacaagagca ggtggcagca ggggaacgtc   1860
ttctcatgct ccgtgatgca tgaggctctg cacaaccact acacgcagaa gagcctctcc   1920
ctgtctccgg gtaaa                                     1935

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<210> SEQ ID NO 191
<211> LENGTH: 1632
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 191

atggccgcag gcggcagtgc gcccgagccc cgcgtcctcg tctgcctcgg ggcgctcctg	60
gccggctggg tcgccgtagg attggaggct gttgtcattg gagaagttca tgagaatgtt	120
actctgcact gtggcaacat ctccgggactg agggggccagg tgacctggta ccggaacaac	180
tcggagcctg tcttccttct ctcgcccaac tctagcctcc ggccagctga gcctcgcttc	240
tctctagtagg atgccacctc cctgcacatt gaatcgctga gcctgggaga tgagggaatc	300
tacacctgcc aggagatcct gaatgtgact cagtgggtcc aagtgtggct gcagggtggc	360
aatccccctc catcagctcc ccagtgtctg gcacagatgg catcaggatc gttcatgttg	420
cagcttacct gtcgctggga tgggggatac cctgacctg acttcctgtg gatagaagag	480
ccaggagggtg taatcgtggg gaagtcaaag ctgggggtgg aaatgctgag cgagtccag	540
ctgtcggatg gcaagaagtt caagtgtgtt acaagccaca tagttgggcc agagtcgggc	600
gccagctgca tgggtcagat caggggtccc tcccttctct ctgagcccat gaagacttgc	660
ttcactgggg gcaatgtgac gcttacatgc caggtgtctg gggcctaccc ccctgccaa	720
atcctgtggc tgaggaaact taccagccc gaggtgatca tccagcctag cagccgccat	780
ctcattaccc aggatggcca gaactccacc ctactatcc acaactgtc ccaggacctg	840
gatgagggtc actacatctg ccgagctgac agccctgtag gggtagaggga gatggaaatc	900
tggctgagtg tgaagaacc tttaaatac gggggggagc ccaaatcttc tgacaaaact	960
cacacatgcc caccgtgcc agcacctgaa ctccctgggg gaccgtcagt ctctctcttc	1020
cccccaaac ccaaggacac cctcatgac tcccggaccc ctgaggteac atgcgtgggtg	1080
gtggacgtga gccacgaaga cctgaggtc aagttcaact ggtacgtgga cggcgtggag	1140
gtgcataatg ccaagacaaa gccgcgggag gagcagtaca acagcacgta ccgtgtggtc	1200
agcgtcctca ccgtcctgca ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc	1260
tccaacaaag cctcccccag ccccatcgag aaaaccatct ccaagccaa agggcagccc	1320
cgagaaccac aggtgtacac cctgccccca tcccgggatg agctgaccaa gaaccaggtc	1380
agcctgacct gcctggctca aggcctctat cccagcgaca tcgccgtgga gtgggagagc	1440
aatgggcagc cggagaacaa ctacaagacc acgcctcccg tgctggactc cgacggctcc	1500
ttcttctct acagcaagct caccgtggac aagagcaggt ggcagcaggg gaacgtcttc	1560
tcattgctcc tgatgcatga ggcctgcac aaccactaca cgcagaagag cctctccctg	1620
tctccgggta aa	1632

<210> SEQ ID NO 192

<211> LENGTH: 1386

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 192

atggcgctgc ctccaggccc agccgccttc cggcacacac tgctgtcct gccagccctt	60
ctgagctcag gttgggggga gttggagcca caaatagatg gtcagacctg ggctgagcgg	120
gcacttcggg agaatgaacg ccacgccttc acctgccggg tggcaggggg gcctggcacc	180
cccagattgg cctggatatc ggatggacag ctgcaggagg ccagcacctc aagactgctg	240
agcgtgggag gggaggcctt ctctggaggc accagcacct tcaactgtcac tgcccatcgg	300

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gcccagcatg agctcaactg ctctctgcag gaccccagaa gtggccgatac agccaacgcc	360
tctgtcatcc ttaatgtgca attcaagcca gagattgccc aagtcggcgc caagtaccag	420
gaagctcagg gcccaggcct cctggttgtc ctgtttgccc tggcgctgc caaccgccg	480
gccaatgtca cctggatcga ccaggatggg ccagtgcactg tcaacacctc tgacttctg	540
gtgctggatg cgcagaacta cccctggctc accaaccaca cgggtgcagct gcagctccgc	600
agcctggcac acaacctctc ggtggtggcc accaatgacg tgggtgtcac cagtgcgtcg	660
cttcagccc cagggcttct ggtaccccg gagcccaat cttctgacaa aactcacaca	720
tgccaccgt gcccagcac tgaactctg gggggaccgt cagtcttct cttccccca	780
aaaccaagg acaccctcat gatctcccgg acccctgagg tcacatgcgt ggtggtggac	840
gtgagccacg aagacctga ggtcaagtc aactggtacg tggacggcgt ggaggtgcat	900
aatgccaaga caaagccgcg ggaggagcag tacaacagca cgtaccgtgt ggtcagcgtc	960
ctcaccgtcc tgcaccagga ctggctgaat ggcaaggagt acaagtgcga ggtctccaac	1020
aaagccctcc cagcccccct cgagaaaacc atctccaaag ccaagggca gcccagagaa	1080
ccacaggtgt acaccctgcc cccatcccgg gatgagctga ccaagaacca ggtcagcctg	1140
acctgcctgg tcaaggctt ctatcccagc gacatcgccg tggagtggga gagcaatggg	1200
cagccggaga acaactacaa gaccacgct cccgtgctgg actccgacgg ctcttcttc	1260
ctctacagca agctcaccgt ggacaagagc aggtggcagc aggggaacgt cttctcatgc	1320
tccgtgatgc atgaggctct gcacaaccac tacacgcaga agagcctctc cctgtctccg	1380
ggtaaa	1386

<210> SEQ ID NO 193
 <211> LENGTH: 1329
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polynucleotide

 <400> SEQUENCE: 193

atggcgctgt tggcggcgg gctctccaga gggctgggct cccaccggc cggcgaggc	60
cgggacgcgg tcgtcttctg gtggcttctg cttagcacct ggtgcacagc tcctgccagg	120
gcatccagg tgaccgtgtc caaccctac cacgtggga tcctcttcca gctgtgacc	180
ctgccctgta cctaccagat gacctcgacc cccacgcaac ccacgtcat ctggaagtac	240
aagtctttct gccgggaccg catcgccgat gccttctccc cggccagcgt cgacaaccag	300
ctcaatgccc agctggcagc cgggaaccca ggctacaacc cctacgtcga gtgccaggac	360
agcgtgcgca ccgtcagggc cgtggccacc aagcagggca acgtgtgac cctgggagat	420
tactaccagg gccggaggat taccatcacc ggaaatgctg acctgacctg tgaccagacg	480
gcgtgggggg acagtgtgtg gtattactgc tccgtggtct cagcccagga cctccagggg	540
aacaatgagg cctacgcaga gctcatcgtc cttggggagg cctcaggggt ggctgagctc	600
ttacctggtt ttcaggcggg gcccatagaa gacgagccca aatcttctga caaaactcac	660
acatgcccac cgtgccacgc acctgaactc ctggggggac cgtcagctct cctcttcccc	720
ccaaaaccca aggacacct catgatctcc cggacccctg aggtcacatg cgtgggtgtg	780
gacgtgagcc acgaagacc tgaggtaag ttcaactggt acgtggacgg cgtggagggtg	840
cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc	900

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gtcctcaccg tectgcacca ggactggctg aatggcaagg agtacaagtg caaggtctcc	960
aacaaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga	1020
gaaccacagg tgtacacct gcccccatcc cgggatgagc tgaccaagaa ccaggtcagc	1080
ctgacctgcc tgggtcaaagg cttctatccc agcgacatcg ccgtggagtg ggagagcaat	1140
gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga cggctccttc	1200
ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtctctca	1260
tgctccgtga tgcattgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct	1320
ccgggtaaa	1329

<210> SEQ ID NO 194

<211> LENGTH: 1272

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 194

atggcgctgt tggccggcgg gctctccaga gggctgggct ccccccggc cgccgcaggc	60
cgggacgcgg tcgtcttcgt gtggtctctg cttagcacct ggtgcacagc tctgccagg	120
gccatccagg tgaccgtgtc caaccctac cacgtggtga tctctctcca gcctgtgacc	180
ctgccctgta cctaccagat gacctcgacc cccacgcaac ccatcgctcat ctggaagtac	240
aagtctttct gccgggaccg catcgccgat gccttctccc cggccagcgt cgacaaccag	300
ctcaatgccc agctggcagc cgggaacca ggctacaacc cctacgtcga gtgccaggac	360
agcgtgcgca ccgtcagggt cgtggccacc aagcagggca acgctgtgac cctgggagat	420
tactaccagg gccggaggat taccatcacc ggaaatgctg acctgacctt tgaccagacg	480
gcgtgggggg acagtgggtg gtattactgc tccgtggtct cagcccagga cctccagggg	540
aacaatgagg cctacgcaga gctcatcgtc cttgacgagc ccaaattctc tgacaaaact	600
cacacatgcc caccgtgccc agcacctgaa ctctgggggg gaccgtcagt ctctctcttc	660
ccccaaaac ccaaggacac cctcatgate tcccggaccc ctgaggtcac atgcgtggtg	720
gtggacgtga gccacgaaga ccttgaggtc aagttcaact ggtacgtgga cggcgtggag	780
gtgcataatg ccaagacaaa gccgcgggag gagcagtaca acagcacgta ccgtgtggtc	840
agcgtcctca ccgtcctgca ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc	900
tccaacaaag cctctccagc ccccatcgag aaaaccatct ccaaagccaa agggcagccc	960
cgagaaccac aggtgtacac cctgccccca tcccgggatg agctgacca gaaccaggtc	1020
agcctgacct gcctggtdaa aggcctctat cccagcgaca tcgcgtgga gtgggagagc	1080
aatgggcagc cggagaacaa ctacaagacc acgcctcccc tgctggactc cgacggctcc	1140
ttctctctct acagcaagct caccgtggac aagagcaggt ggcagcaggg gaacgtcttc	1200
tcatgctccg tgatgcatga ggcctctgac aaccactaca cgcagaagag cctctccctg	1260
tctccgggta aa	1272

<210> SEQ ID NO 195

<211> LENGTH: 2295

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 195

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atggcgctgt	tggccggcgg	gctctccaga	gggtggggt	cccacccggc	cgccgcaggc	60
cgggacgcgg	tcgtcttcgt	gtggcttctg	cttagcacct	ggtgcacagc	tcctgccagg	120
gccatccagg	tgaccgtgtc	caacccttac	cacgtgggtg	tcctcttcca	gcctgtgacc	180
ctgccttgta	cctaccagat	gacctcgacc	cccacgcaac	ccatcgctcat	ctggaagtac	240
aagtctttct	gccgggaccc	catcgccgat	gccttctccc	cggccagcgt	cgacaaccag	300
ctcaatgccc	agctggcagc	cgggaaccca	ggctacaacc	cctacgtcga	gtgccaggac	360
agcgtgcgca	ccgtcagggt	cgtggccacc	aagcagggca	acgtgtgac	cctgggagat	420
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gcgtgggggg	acagtgtgtg	gtattactgc	tccgtgggtc	cagcccagga	cctccagggg	540
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<210> SEQ ID NO 196
<211> LENGTH: 2292
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 196

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<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

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<210> SEQ ID NO 198

<211> LENGTH: 2352

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polynucleotide

<400> SEQUENCE: 198

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What is claimed is:

1. A method of treatment of cancer, comprising administering a pharmaceutically active amount of a monoclonal or polyclonal antibody or an antigen binding fragment thereof comprising an antigen binding site that binds specifically to an extracellular domain of a polypeptide, consisting essentially of 108, 145, or 170 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NOs: 11, 13, 15-18, 67, 143, or comprising an antigen binding site that binds specifically to a polypeptide consisting of an amino acid sequence set forth in any one of SEQ ID NOs: 10, 12, 14, 22, 47-50 and 102, to the subject in need of treatment thereof.

2. The method of claim 1, wherein the antibody is selected from the group consisting of a fully human antibody, chimeric antibody, humanized antibody, primatized antibody, Fab, Fab', F(ab')₂, F(ab'), F(ab), Fv, scFv fragment and minimal recognition unit.

3. The method of claim 2, wherein the antibody is coupled to a moiety selected from the group consisting of a drug, a radionuclide, an enzyme, a toxin, a therapeutic agent, and a chemotherapeutic agent.

4. The method of claim 1, wherein the treatment is combined with administering to the subject another moiety or therapy useful for treating cancer.

5. The method of claim 4, wherein the therapy is radiation therapy, antibody therapy, chemotherapy, photodynamic therapy, adoptive T cell therapy, Treg depletion, surgery or a combination therapy with conventional drugs.

6. The method of claim 4, wherein the moiety is selected from the group consisting of a cytotoxic drug, a tumor vaccine, an antibody selected from the group consisting of bevacizumab, erbitux and immunostimulatory antibodies; peptides, pepti-bodies, small molecules, a chemotherapeutic agent, interferons, interleukins, growth hormones, folic acid, vitamins, minerals, aromatase inhibitors, RNAi, histone deacetylase inhibitors, and proteasome inhibitors.

7. The method of claim 1, wherein the cancer is selected from the group consisting of breast cancer, cervical cancer, ovary cancer, endometrial cancer, melanoma, bladder cancer, lung cancer, pancreatic cancer, colon cancer, prostate cancer, leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, B-cell lymphoma, Burkitt's lymphoma, multiple myeloma, Hodgkin's lymphoma, Non-Hodgkin's lymphoma,

myeloid leukemia, acute myelogenous leukemia (AML), chronic myelogenous leukemia, thyroid cancer, thyroid follicular cancer, myelodysplastic syndrome (MDS), fibrosarcomas and rhabdomyosarcomas, melanoma, uveal melanoma, teratocarcinoma, neuroblastoma, glioma, glioblastoma, benign tumor of the skin, keratoacanthomas, renal cancer, anaplastic large-cell lymphoma, esophageal squamous cells carcinoma, hepatocellular carcinoma, follicular dendritic cell carcinoma, intestinal cancer, muscle-invasive cancer, seminal vesicle tumor, epidermal carcinoma, spleen cancer, bladder cancer, head and neck cancer, stomach cancer, liver cancer, bone cancer, brain cancer, cancer of the retina, biliary cancer, small bowel cancer, salivary gland cancer, cancer of uterus, cancer of testicles, cancer of connective tissue, prostatic hypertrophy, myelodysplasia, Waldenstrom's macroglobinaemia, nasopharyngeal, neuroendocrine cancer, myelodysplastic syndrome, mesothelioma, angiosarcoma, Kaposi's sarcoma, carcinoid, oesophagogastric, fallopian tube cancer, peritoneal cancer, papillary serous müllerian cancer, malignant ascites, and gastrointestinal stromal tumor (GIST), and wherein the cancer is non-metastatic, invasive or metastatic.

8. The method of claim 1, wherein the cancer is selected from the group consisting of liver cancer, prostate cancer, lung cancer, ovarian cancer, colon cancer, breast cancer, stomach cancer and renal cancer.

9. A method of using a monoclonal or polyclonal antibody or an antigen binding fragment thereof comprising an antigen binding site that binds specifically to an extracellular domain of a polypeptide, consisting essentially of 108, 145, or 170 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NOs: 11, 13, 15-18, 67, 143, or comprising an antigen binding site that binds specifically to a polypeptide consisting of an amino acid sequence set forth in any one of 12, 14, 47-50, 10, 22 or 102, as a cancer vaccine adjuvant, comprising administration to a patient an immunogenic amount of a tumor associated antigen preparation of interest; and the cancer vaccine adjuvant in a formulation suitable for immunization, wherein the immune response against the tumor associated antigen in the presence of the cancer vaccine adjuvant is stronger than in the absence of the cancer vaccine adjuvant.

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10. The method of claim 6, wherein the antibody is selected from the group consisting of bevacizumab and erbitux.

11. The method of claim 6, wherein the chemotherapeutic agent is selected from the group consisting of a cytotoxic agent and a cytostatic agent.

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12. The method of claim 6, wherein the chemotherapeutic agent is selected from the group consisting of paclitaxel, cisplatin, vinorelbine, docetaxel, gemcitabine, temozolomide, irinotecan, 5FU and carboplatin.

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